CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 19-839/S-035
20-990/S-003

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA:	19-839/S-035 20-990/S-003*
SPONSOR:	Pfizer Pharmaceuticals Group
DRUG:	Zoloft (Sertraline HCl) Tablets and Oral Concentrate
DATE OF DOCUMENT:	5/25/2001
DATE RECEIVED:	5/29/2001

I. REVIEW:

These supplemental new drug applications listed above provide for the use of Zoloft (sertraline HCl) tablets and Zoloft (sertraline HCl) oral concentrate for the long-term treatment of post-traumatic stress disorder (PTSD).

In response to our approvable letter, the sponsor has submitted the updated version of the proposed package insert taking into account the comments received from us. All of the suggestions received from the Agency were incorporated into the labeling with the exception of the following few items:

1. Under INDICATIONS AND USAGE, PTSD, in the fourth and final paragraph of this subsection, the term [redacted] was deleted in the first sentence of this paragraph because the patients that entered the open label 24-week treatment had already completed a 12-week placebo-controlled trial prior to entering the open label treatment.

2. Under DOSAGE AND ADMINISTRATION, Maintenance Treatment, the three paragraphs suggested by the Agency were incorporated with a few minor revisions.

   In the third sentence of the first paragraph of this section under the sub-heading of Depression, the term [redacted] was deleted. It is Pfizer's position that this term is unnecessary, as the data to which it refers is well described in the previous sentence. The phrase " [redacted] ' was deleted from the fourth sentence of the first paragraph of this section because the statement is repetitive and repeats what was previously been said about the dosing range in the same paragraph.

   In the third and fourth sentence of the second paragraph of this section under the sub-heading of Posttraumatic Stress Disorder, the same revisions were incorporated as described in the paragraph above under the sub-heading Depression.

I have compared these changes with our letter and believe the sponsors summary above is accurate.

II. RECOMMEDATION:

I feel the sponsors changes are not significant and recommend we accept the labeling submitted.

Earl D. Hearst, M.D.
Medical Reviewer
HFD-120
cc: [redacted]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Earl Hearst
6/29/01 11:13:10 AM
MEDICAL OFFICER

Thomas Laughren
7/3/01 02:51:54 PM
MEDICAL OFFICER
I agree that this supplement can now be approved.--TPL

APPEARS THIS WAY
ON ORIGINAL

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA:	19-839/20-990
Sponsor:	Pfizer
Clock Date:	6/1/00

Drug Name

Generic Name	sertraline
Trade Name	Zoloft

Drug Characterization

Pharmacological Category: Antidepressant
Proposed Indication: Post Traumatic Stress Disorder (PTSD)
Relapse Prevention
NDA Classification: 1S
Dosage Forms, Strengths, and Routes of Administration:
Oral Tablets 25mg, 50mg, 100mg

Reviewer Information

Clinical Reviewer: Earl D. Hearst, M.D.
Review Completion Date: 01/12/01

1.0 Material Reviewed

The sponsor has provided 25 Volumes, a CD disk summarizing these volumes, SAS data sets for this submission and financial disclosure information.

I have reviewed these volumes including financial disclosure information and all narratives for patients meeting the criteria for adverse events leading to discontinuation and serious adverse events including vital signs, weight, laboratory analytes, ECG intervals and heart rate.

2.0 Background

2.1 Indication

The indication section is largely unchanged except as follows:

The efficacy of ZOLOFT in the long-term treatment of PTSD was demonstrated for up to 52 weeks, in a design which consisted of 24 weeks open-label treatment followed by 28 weeks of placebo-controlled double-blind treatment. In the final phase of treatment, patients randomized to ZOLOFT had a significantly lower rate of discontinuation due to relapse or insufficient clinical response than did patients randomized to placebo. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

2.2 Related INDs and NDAs

Zoloft has been submitted to us under the following INDs.

IND#	Filing Date	Drug
[redacted]		
[redacted]		
[redacted]		

2.3 Administrative History

Pfizer initially developed sertraline hydrochloride (Zoloft) as

an antidepressant. An NDA (#19-839) for its use in the treatment of depression was approved on December 30, 1991. Supplemental NDAs for the use of sertraline in the treatment of Obsessive-Compulsive Disorder (OCD), Panic Disorder and Post-Traumatic Stress Disorder (PTSD) were approved on October 25, 1996, July 8, 1997 and December 7, 1999, respectively. The relapse prevention supplement was submitted on June 1, 2000.

2.4 Directions for Use

This section is unchanged with the exception of the expanded indication reproduced above and in the labeling sections.

3.0 Chemistry

There are no changes in this section.

4.0 Preclinical Pharmacology

There are no changes in this section.

5.0 Description of Clinical Data Sources

5.1 Primary Development Program

5.1.1 Study Type and Design/Patient Enumeration

There were two studies in this submission which I will describe below.

Study 672, the open-label extension, was designed to evaluate the safety and efficacy of open-label sertraline in subjects who completed 12 weeks of double-blind treatment with sertraline or placebo in Study 671 or 682 (previously reviewed).

Study 703 was designed to evaluate the comparative safety and efficacy of sertraline and placebo in the prevention of PTSD relapse in subjects who completed and responded to 24 weeks of open-label sertraline treatment in Study 672.

In this 28-week, multicenter, double-blind flexible-dose study, the long-term safety and efficacy of sertraline were evaluated in outpatients who completed Study 672 and responded to

sertraline at their last two consecutive visits in Study 672. Subjects in Study 703 originally met criteria for a DSM-III-R diagnosis of PTSD at the beginning of Studies 671 and 682.

Of the 380 subjects randomized in the feeder studies, Studies 671 and 682, 275 (72%) completed 12 weeks of double-blind treatment with sertraline or placebo. Of these, 252 (128 sertraline, 124 placebo) entered Study 672 in which they received open-label sertraline. All 252 subjects provided follow-up safety data and 155/252 (62%) completed the study. Two hundred forty nine subjects were included in the intent-to-treat analysis. Of the 252 subjects entered in Study 672, 139 (55%) completed 24 weeks of open-label treatment and were considered responders. Of these, 96 subjects were randomized to double-blind treatment (46 sertraline, 50 placebo) in Study 703 and were evaluable for safety.

The sponsor did not integrate data from the open study 672 with the double-blind controlled study 703. From this point on I will deal primarily with Study 703 for relapse prevention but will include serious safety adverse events and adverse events leading to dropout from study 672 where appropriate in the safety sections.

5.1.2 Demographics

The study population for 703 was 78% female (36/46) in the sertraline treatment group and 62% (31/50) in the placebo group. Subjects were mainly white, with 87% (40/46) white, 9% (4/46) black, and 4% (2/46) Asian subjects in the sertraline group and 96% (48/50) white and 4% (2/50) Asian subjects in the placebo group. The mean age was 45 and 42 years in the sertraline and placebo groups, respectively. The mean duration of illness in the sertraline group was 12 years with a mean time from traumatic event of 19 years; in the placebo group, the mean duration of illness was 14 years and the mean time from traumatic event was 19 years. The most common comorbid Axis I diagnosis (captured using the SCID at the baseline of the feeder studies) was depression, in 35% (16/46) of sertraline subjects and 44% (22/50) of placebo subjects. There was no comorbid Axis I diagnosis for 50% (23/46) of sertraline subjects and 48% (24/50) of placebo subjects. Baseline characteristics were also analyzed separately for males and females. The only statistically significant difference between treatment groups within sex was for age in males ($p = 0.05$: male sertraline ($N = 10$) and placebo ($N = 19$) subjects were 50 and 41 years.

The most common traumatic event was physical or sexual assault, which occurred in 64% of females (43/67), 34% of males (10/29),

52% of subjects in the sertraline group (24/46), and 58% of subjects in the placebo group (29/50).

5.1.3 Extent of Exposure (dose/duration)

Table 3.1 provides a summary of duration of double-blind therapy. The mean duration of therapy in the sertraline and placebo groups was 146 and 105 days.

TABLE 3.1: DURATION (DAYS) OF DOUBLE-BLIND THERAPY FOR SAFETY ANALYZABLE SUBJECTS

	SERTRALINE	PLACEBO
NUMBER OF SUBJECTS	46	50
DURATION CATEGORY (DAYS)		
1 - 7	2	1
8 - 14	0	3
15 - 28	3	7
29 - 42	3	10
43 - 56	2	4
57 - 70	2	2
71 - 84	0	1
85 - 98	3	1
99 -112	1	0
113 -126	1	0
127 -140	0	0
141 -154	0	0
155 -168	0	0
169 -182	0	1
183 -196	11	7
>= 197	18	13
MEAN DURATION (DAYS)	146.2	105.3
RANGE (DAYS)	1-213	5-234

The mean daily dose of sertraline and the equivalent dose of placebo administrated by study week is presented in Table 3.2 in dosing section for Study 703. At endpoint, the mean daily dose received by safety analyzable sertraline and placebo subjects was 137 mg and 145 mg, respectively. For Weeks 27-28, sertraline and placebo subjects who completed the study received a mean daily dose of 134 mg and 120 mg, respectively.

For more on dosing please see Study 703 dosing section to follow.

5.1.4 Disposition

96 subjects were randomized to double-blind treatment (46 sertraline, 50 placebo) in Study 703 and were evaluable for safety. Of the 96 safety evaluable subjects, 48 completed the study (28 sertraline, 20 placebo). Two sertraline subjects did not have follow-up efficacy data. In addition, the intent-to-treat analysis
for efficacy excludes 10 subjects (6 sertraline, 4 placebo) from Study Site 96N0207 (Investigator: Bharat Nakra). Accordingly, the intent-to-treat analysis is based on 84 subjects (38 sertraline and 46 placebo). See statistical analysis section and section 7.2.2.

5.2 Secondary Sources

5.2.1 Non-IND Studies

There are no non-IND studies to be considered for this review.

5.2.2 Post-Marketing Experience

There is no available post marketing experience related to relapse prevention.

5.2.3 Literature

The database of Pfizer-sponsored trials was searched by the sponsor for studies in the prevention of PTSD relapse that were either completed or ongoing as of February 23, 2000. No studies were identified. The sponsor's search of existing literature through February 23, 2000 for studies in the prevention of PTSD relapse did not identify any studies.

5.3 Adequacy of Clinical Experience

The exposure to sertraline appears to be of an adequate duration and dosage and the clinical experience is otherwise satisfactory.

5.4 Data Quality and Completeness

The data quality appears to be adequate and complete in that the specified scales and tests were appropriate, performed and results collected and analyzed.

6.0 Summary of Human Pharmacokinetics

There is nothing new in this section to report.

7.0 Efficacy Findings

7.1 Overview of Studies Pertinent to Efficacy (STUDY 703)

Dosing.

The mean daily dose of sertraline and the equivalent dose of placebo administrated by study week is presented in Table 3.2. At endpoint, the mean daily dose received by safety analyzable sertraline and placebo subjects was 137 mg and 145 mg, respectively. For Weeks 27-28, sertraline and placebo subjects who completed the study received a mean daily dose of 134 mg and 120 mg, respectively.

TABLE 3.2: MEAN DAILY DOSE BY VISIT WEEK BY TREATMENT GROUP FOR SAFETY ANALYZABLE SUBJECTS

Visit Week	Sertraline (mg)			Placebo (mg equivalent)		
	N	Mean	SD	N	Mean	SD
Week 2	46	136.5	54.2	50	138.7	57.8
Week 4	44	135.9	53.0	45	136.1	58.4
Week 6	38	137.5	58.1	31	132.2	57.5
Week 8	37	138.3	54.6	28	125.9	63.7
Week 10	35	135.7	55.3	24	130.1	63.0
Week 12	33	136.2	60.1	23	129.0	61.5
Week 14	31	134.4	58.7	22	129.2	63.2
Week 16	29	132.7	60.8	21	129.0	65.4
Week 18	30	131.9	59.4	21	127.5	64.5
Week 20	28	137.4	58.7	21	118.8	68.1
Week 22	29	132.8	61.0	20	125.7	65.1
Week 24	29	133.5	59.6	21	126.5	63.7
Week 26	29	129.3	59.6	20	122.4	63.3
Week 28	28	133.8	58.7	20	119.8	63.3
Endpoint	46	137.0	51.9	50	145.1	57.5

Note: The average dose was calculated for each subject at every visit. The mean of the subjects' average doses was determined by visit.

Primary Efficacy Variables.

For Study 703 the analyses of efficacy included: (1) the time to relapse and the rate of relapse (2) the time to relapse or discontinuation due to insufficient clinical response and the rate of relapse or discontinuation due to insufficient clinical response and (3) the time to acute exacerbation of PTSD and the rate of acute exacerbation of PTSD.

The secondary efficacy parameters were the CAPS-2 17-item total severity score, CAPS-2 symptom clusters and global ratings, Impact of Event (IES) total score, IES symptom clusters, Davidson Scale total, Davidson Scale symptom clusters, CGI-S and CGI-I ratings, Hamilton Depression Scale (Ham-D) and Q-LES-Q.

Statistical Analysis:

The main objectives of the data analysis in this study was to evaluate rates of clinical failure as measured by relapse and relapse/discontinuation due to insufficient clinical response, as well as by acute exacerbation of PTSD, and to evaluate long-term safety in sertraline-treated subjects. Subjects who took at least one dose of study drug and provided any follow-up safety data were considered safety analyzable. Safety analyzable subjects with available post-baseline efficacy data were included in the intent-to-treat analysis of efficacy.

All statistical tests were two-sided and performed at the 0.05 level of significance. No adjustments for multiple comparisons were made.

Relapse rates were summarized by treatment as the proportion of subjects who experienced the event. Comparisons between treatment groups were made using Fisher's exact test. The same summaries and analyses were provided for the proportion of subjects who discontinued the study due to either relapse or insufficient clinical response as well as for the proportion of subjects who experienced acute exacerbation of PTSD. The odds ratios and their 95% confidence intervals were used to evaluate relapse, relapse or discontinuation due to insufficient clinical response, and acute exacerbation rates in the placebo treatment group relative to the sertraline treatment group. Relapse, insufficient clinical response, and acute exacerbation rates were also summarized by gender and traumatic event. All hypothesis tests were performed using the Type III sums of squares from the SAS GLM procedure.

STUDY RESULTS:

Study 672

Study 672 is an open study and the efficacy results can not be interpreted with any confidence. The sponsor however makes the following points about the study.

The primary and secondary efficacy analyses showed statistically significant ($p \leq 0.05$) improvement in Study 672. From the Study 672 baseline to the Study 672 endpoint, there was statistically significant improvement for all intent-to-treat subjects, males, and females.

Significant improvement was seen in Study 672 in subjects who received placebo in the feeder studies as well as in those subjects who received sertraline in the feeder studies; the extent of improvement was greater in those who received placebo in the feeder studies. Males and females had a similar extent of improvement in these analyses. All subjects, males, and females who received sertraline in the feeder studies showed significant mean improvement in Study 672 from the baseline of the feeder studies to the Study 672 endpoint. There was also a substantial increase in response rate at the endpoint to Study 672 as compared to the baseline of this study.

The following table prepared by the sponsor shows the efficacy results of study 672.

Table A. Summary of Change in Parameters from PTSD-Specific Rating Scales: CAPS-2 Total Severity Score, IES Total Score, and Davidson Scale Total Score[a]

	Baseline of Feeder Studies to Endpoint of Study 672[b,c]			Baseline of Study 672 to Endpoint of Study 672[b,d]		
Subjects	Baseline	Change	%Change	Baseline	Change	%Change
CAPS-2 (17-Item Total Severity Score)						
All Subjects	43.42	-15.57	-35.9%	75.87	-48.10	-63.4%
Females	43.95	-15.81	-36.0%	77.02	-50.77	-65.9%
Males	42.01	-14.93	-35.5%	72.53	-40.31	-55.6%
IES (Total Score)						
All Subjects	20.81	-7.46	-35.8%	38.39	-25.07	-65.3%
Females	21.12	-7.60	-36.0%	38.20	-25.59	-67.0%
Males	19.95	-7.08	-35.5%	38.97	-23.53	-60.4%
Davidson Scale (Total Score)						
All Subjects	43.13	-13.41	-31.1%	73.39	-43.21	-58.9%
Females	42.79	-12.46	-29.1%	74.10	-45.26	-61.1%
Males	44.06	-16.02	-36.4%	71.26	-37.04	-52.0%

[a]CAPS-2 total severity score and IES total score are primary assessments; Davidson Scale total score is a secondary assessment. [b]Negative change indicates improvement. [c]For all subjects enrolled in Study 672. [d]For subjects randomized to sertraline in the feeder studies who were enrolled in Study 672.

Study 703

Investigators

96-N-0185 Gregory M. Asnis , M.D.
96-N-0186 Dewleen Baker, M.D.
96-N-0187 Robert Bielski, M.D.
96-N-0188 Kathleen Brady, Ph.D., M.D.
96-N-0189 Jonathan Davidson, M.D.
96-N-0190 Susanna Goldstein, M.D.

96-N-0191 Mark Hegel, Ph.D.
96-N-0192 Jonathan M. Himmelhoch, M.D.
96-N-0193 Henry Lahmeyer, M.D.
96-N-0194 Peter Londborg, M.D.
96-N-0195 Teri Pearlstein, M.D.
96-N-0196 Murray Rosenthal, D.O.
96-N-0197 Barbara Rothbaum, Ph.D.
96-N-0198 Ward Smith, M.D.
96-N-0199 Jon Bell, M.D.
96-N-0201 Lynn Cunningham, M.D.
96-N-0202 Eugene DuBoff, M.D.
96-N-0203 David Goldstein, M.D.
96-N-0204 Wayne Goodman, M.D.
96-N-0205 Jon F. Heiser, M.D.
96-N-0206 Richard Maddock, M.D.

96-N-0208 William Patterson, M.D.
96-N-0210 Jeffery Rausch, M.D.

Objectives

The long-term safety and efficacy of sertraline were the objectives evaluated in this relapse prevention study.

Study Design

This was a 28-week, multicenter, double-blind, flexible-dose, continuation study. It was designed to evaluate the comparative safety and efficacy of sertraline and placebo in the prevention of PTSD relapse in outpatients who completed and responded to 24 weeks of open-label sertraline treatment in Study 672.

Rating Scales

The CAPS-2 total severity score was computed as the sum of the frequency and intensity of each of the first 17 items, corresponding to the DSM-III-R diagnostic symptom criteria for PTSD. Both frequency and intensity for each item were assigned numeric values of 0, 1, 2, 3, and 4 (increasing with higher numbers). The investigator rated the subject's condition within the following three symptom clusters:

The subject responded to a series of 15 statements consisting of seven intrusion items and eight avoidance items by assigning numeric values of 0, 1, 3 or 5 to each one (0 = not at all, 1

= mild, 3 = moderate, or 5 = severe) to describe his or her symptoms during the past week. Analysis of these 15 items constitutes the total score of the IES.

For CGI Severity of Illness, the investigator rated the subject in response to the following question, "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" The ratings were: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; and 7 = among the most severely ill.

For CGI Global Improvement (whether or not due to drug treatment), the investigator rated the subject in response to the following question, "Compared to his/her condition at the beginning of the initial double-blind study (Protocols 95CE21-0671 or 96CE21-0682), how much has he/she changed?" The ratings were: 1 = very much improved, 2 = much improved, 3 =minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse.

Analysis

There were two primary efficacy analyses specified in the analysis plan: (1) the time to relapse and the rate of relapse and (2) the time to relapse or discontinuation due to insufficient clinical response and the rate of relapse or discontinuation due to insufficient clinical response. In addition, the time to the first acute exacerbation of PTSD and the rate of acute exacerbation of PTSD were evaluated. Data for evaluation of the primary efficacy parameters were based on the CAP-2 17-item total severity score and CGI-I, described below, as well as on the investigator's opinion of the subject's clinical condition.

7.2.1 General Protocol Deviations

Subject 96N00197/1009, a male placebo-treated subject, was not a responder at the Study 703 baseline and therefore did not meet entrance criteria. He remained in the study and received study drug for 5 days and was discontinued due to an adverse event, increased sweating.

Two subjects missed dosing for 4 or more consecutive days during the study: 96N0185/1019 (randomized to sertraline) and 96N0191/1015 (randomized to placebo).

The three subjects reported above were included in the efficacy analyses. None were discontinued due to protocol violations.

One subject (96N0203/1085) was discontinued after 1 day of sertraline treatment because he was not a sertraline responder and therefore did not meet entrance criteria. He was not included in the efficacy analyses.

7.2.2 Study Site

On April 26, 1999, Pfizer was notified by [redacted] that an audit of the study site of [redacted] was conducted to investigate allegations of scientific misconduct reported while Pfizer Study 703 was ongoing. The Committee concluded from its review of [redacted] site that during the time Study 703 was ongoing, scientific misconduct occurred, and dated back to December 1995. Pfizer has not independently confirmed any of these findings. Therefore, the intent-to-treat analysis of this study report excludes subjects from [redacted] site.

Study Outcome

Patient Disposition

As shown in appendix table 4.1, 48 of 96 subjects withdrew from treatment during the study. The discontinuation rates for the sertraline and placebo groups were 39% (18/46) and 60% (30/50), respectively. The most frequent reason for discontinuation in the sertraline group was insufficient clinical response (11% [5/46] of sertraline subjects vs. 20% [10/50] of placebo subjects). In the placebo group, the most common reason for discontinuation was that subjects met relapse criteria (28% [14/50] of placebo subjects vs. 7% [3/46] of sertraline subjects).

Of the 96 safety-evaluable subjects, 48 completed the study: 28 (61%) in the sertraline group and 20 (40%) in the placebo group. Two sertraline subjects (No. 96N0194/1064 and 96N0203/1085) did not have follow-up efficacy data, and so were not included in the intent-to-treat efficacy analysis. Therefore, the overall intent-to-treat population included 94 subjects, 44 who were treated with sertraline and 50 who were treated with placebo. However,10 subjects, 6 who were treated with sertraline and 4 who were treated with placebo, in Study Site ——— (Investigator: ——————— are not included in the intent-to-treat analysis. They are included in the analyses of safety. The efficacy analysis includes 84 subjects, 38 who were treated with sertraline and 46 who were treated with placebo.

Demographics

See previous demographic section.

Dosing Information

See previous dosing section.

Table 3.1 (section 5.1.3)provides a summary of duration of double-blind therapy. The mean duration of therapy in the sertraline and placebo groups was 146 and 105 days. The mean daily dose of sertraline and the equivalent dose of placebo administrated by study week is presented in Table 3.2 (section 7.1). At endpoint, the mean daily dose received by safety analyzable sertraline and placebo subjects was 137 mg and 145 mg, respectively. For Weeks 27-28, sertraline and placebo subjects who completed the study received a mean daily dose of 134 mg and 120 mg, respectively.

Concomitant Medications

Appendix table 9 provides a listing of concomitant medications taken during double-blind therapy. In the sertraline and placebo groups, respectively, 42 (91%) and 39 (78%) subjects took one or more concomitant medications. The most commonly used concomitant medications in the sertraline and placebo treatment groups were NSAIDs.

RESULTS:

The results leave little doubt that relapse prevention was demonstrated. I will reiterate the key results in this submission that make the case for my statement above.

The sponsor has provided data that shows significantly more subjects in the placebo group than in the sertraline group relapsed, relapsed/discontinued due to an insufficient clinical response, or experienced an acute exacerbation of PTSD. The time to these occurrences was also significantly shorter in the placebo group. They have a variety of measures which support this conclusions described below.

The number and percent of responders at each visit after baseline are presented by gender and treatment group in Table 5.5.1. As shown in Table 5.5.2, the proportions of responders at the endpoint for Study 703 were 78.9% (30/38) and 45.7% (21/46) in the sertraline and placebo groups, respectively. The odds of responding at endpoint were 4.464 times greater in the sertraline group than in the placebo group. The treatment difference in the response rate was statistically significant (p = 0.0032, Fisher's exact test).

The proportions of responders at any time after baseline were 94.7% (36/38) and 65.2% (30/46) in the sertraline and placebo groups, respectively. The odds of responding at any time after baseline on were 9.6 times greater in the sertraline group than in the placebo group. The treatment difference in the response rate was statistically significant (p = 0.0011, Fisher's exact test).

Kaplan-Meier estimates of the cumulative probabilities of not experiencing an acute exacerbation of PTSD are presented for weekly time intervals by treatment group in appendix Table 5.6.3. The cumulative survival probabilities were higher in the sertraline group than in the placebo group and the treatment difference was statistically significant (p = 0.0003, log-rank test).

Adjusted mean changes for all subjects, females, and males are presented in appendix Tables 5.2.1, 5.2.2, and 5.2.3, respectively. Baseline values (and unadjusted mean values for change at each visit and endpoint) by treatment group within gender are presented in appendix Table 5.4.1. Adjusted mean changes in the CAPS-2 17-item total severity score from baseline to endpoint for all subjects were significantly different (p = 0.001) between treatment groups, with changes in the sertraline and placebo groups of 4.4 (baseline: 14.8) and 20.7 (baseline: 16.1), respectively. Among females, the changes were also significantly different (p = 0.005), with changes in the sertraline and placebo groups of 5.4 (baseline: 14.4) and 22.0 (baseline: 15.8), respectively. Among males, the changes were again significantly different (p = 0.018), with changes in the

sertraline and placebo groups of -12.8 (baseline: 16.1) and 17.5 (baseline 16.6), respectively.

Adjusted mean changes in the IES total score from baseline to endpoint for all subjects were significantly different (p = 0.028) between treatment groups, with changes in the sertraline and placebo groups of 1.1 (baseline: 6.5) and 5.9 (baseline: 7.4), respectively. Among females, the changes approached statistical significance (p = 0.061), with changes in the sertraline and placebo groups of 2.2 (baseline: 5.1) and 7.2 (baseline: 7.5), respectively. Among males, the changes were significantly different (p = 0.043), with changes in the sertraline and placebo groups of -7.0 (baseline: 11.0) and 5.9 (baseline 7.2), respectively.

As shown in Table 5.7.1, the proportions of subjects who relapsed in the sertraline and placebo groups were 5.3% (2/38) and 26.1% (12/46), respectively. The odds of relapse were 6.353 times greater in the placebo group than in the sertraline group. The difference between treatment groups in the relapse rate was statistically significant (p = 0.0166, Fisher's exact test).

The proportions of subjects who relapsed or discontinued due to insufficient clinical response for the sertraline and placebo groups were 15.8% (6/38) and 45.7% (21/46), respectively (Table 5.7.1). The odds were 4.48 times greater in the placebo group than in the sertraline. The treatment difference was statistically significant (p = 0.0047, Fisher's exact test).

The proportions of subjects who had acute exacerbation of PTSD in the sertraline and placebo groups were 15.8% (6/38) and 52.2% (24/46), respectively (Table 5.7.1). The odds of acute exacerbation of PTSD were 5.818 times greater in the placebo group than in the sertraline group. The difference between treatment groups was statistically significant (p = 0.0006, Fisher's exact test).

EFFICACY CONCLUSION STUDY 703

This study demonstrates efficacy by virtue of the Kaplan-Meier estimates and the secondary efficacy variables described below.

Kaplan-Meier estimates of the cumulative survival probability to be relapse-free were higher in the sertraline group than in the

placebo group and the treatment difference was statistically significant (p = 0.0070, log-rank test).

Kaplan-Meier estimates of the cumulative probability of not discontinuing due to relapse or insufficient clinical response were higher in the sertraline group than in the placebo group and the difference between treatment groups was statistically significant (p = 0.0016, log-rank test).

The mean changes for CAPS-2 17-item total severity score, IES total score, Davidson total score, CGI-S, CGI-I, Ham-D, and Q-LES-Q were significantly different between the sertraline and placebo treatment groups, indicating lesser symptom severity with sertraline. A similar pattern was demonstrated in both male and female subjects. Significantly more sertraline subjects than placebo subjects were treatment responders at endpoint or at any time during the study following baseline.

7.3 Summary of Data Pertinent to Important Clinical Issues

7.3.1 Predictors of Response

It seems to me that the small size of this study does not allow any conclusions to be reached regarding demographic predictors of response. It is of note the male and female relapse rates were similar in this study.

Among female subjects, the proportions who relapsed were 6.9% (2/29) and 25.0% (7/28) in the sertraline and placebo groups, respectively. Among male subjects, the proportions were 0% (0/9) and 27.8% (5/18) in the sertraline and placebo groups, respectively.

Among female subjects, the proportions of subjects who discontinued due to relapse or insufficient clinical response were 17.2% (5/29) and 46.4% (13/28) in the sertraline and placebo groups, respectively. Among male subjects, the proportions were 11.1% (1/9) and 44.4% (8/18), respectively.

For females at baseline, remitted responders included 75.9% (22/29) and 75.0% (21/28) in the sertraline and placebo groups, respectively. At endpoint, they included 58.6% (17/29) and 28.6% (8/28), respectively. For males at baseline, remitted responders

included 77.8% (7/9) and 61.1% (11/18) in the sertraline and placebo groups, respectively. At endpoint, they included 88.9% (8/9) and 38.9% (7/18), respectively.

Traumatic events were categorized as natural disaster, serious accident/fire/injury, physical or sexual assault, seeing someone hurt or die, being in a war or combat, or other event. The most common traumatic event was physical or sexual assault, which occurred in 64% of females (43/67), 34% of males (10/29), 52% of subjects in the sertraline group (24/46), and 58% of subjects in the placebo group (29/50). There is no analysis of traumatic event-response interaction in this submission.

7.3.2 Size of Treatment Effect

Adjusted mean changes in the CAPS-2 17-item total severity score from baseline to endpoint for all subjects were significantly different ($p = 0.001$) between treatment groups, with changes in the sertraline and placebo groups of 4.4 (baseline: 14.8) and 20.7 (baseline: 16.1), respectively. Adjusted mean changes in the IES total score from baseline to endpoint for all subjects were
significantly different ($p = 0.028$) between treatment groups, with changes in the sertraline and placebo groups of 1.1 (baseline: 6.5) and 5.9 (baseline: 7.4), respectively.

7.3.3 Choice of Dose

This was a flexible dose study. At endpoint, the mean daily dose received by safety analyzable sertraline and placebo subjects was 137 mg and 145 mg, respectively. For Weeks 27-28, sertraline and placebo subjects who completed the study received a mean daily dose of 134 mg and 120 mg, respectively.

7.3.4 Duration of Treatment

This was a 28-week study following 24 weeks of open label treatment. There is no controlled data beyond that point.

7.4 Financial Disclosure Data

The sponsor was able to obtain data for all primary investigators except [redacted] and [redacted] The sponsor claims due diligence with an inability to obtain financial data [redacted] subinvestigators.

7.5 Conclusions Regarding Efficacy Data

Study 703 offers convincing evidence that sertraline is effective for relapse prevention in patients with PTSD over a 28 week study period. The statistical reviewer John Lawrence Ph.D. agrees with this conclusion. I question the due diligence in being unable to obtain financial data subinvestigators however, of the disclosures obtained I see no reason to conclude that any investigator had a financial interest in the outcome of the studies.

8.0 Safety Findings

8.1 Methods

For the purposes of this submission, a cut-off date of February 23, 2000 was established for reporting of serious adverse events from the AEM database. AEM data cumulative to February 23, 2000 was
reviewed for Studies 672 and 703.

All treatment-emergent adverse events occurring up to 7 days after the last dose of study drug were categorized according to World Health Organization terminology and tabulated regardless of their assessed severity or relationship to study drug. All adverse events reported after the beginning of treatment in double-blind Study 703 were defined as treatment-emergent adverse events. The number and percent of treatment-emergent adverse events were summarized
within each WHO body system, preferred term, and treatment group. They were also summarized by maximum severity and gender. The incidence rates of subjects with any adverse event and of individual adverse events were compared between treatment groups using Fisher's exact test. The same comparisons were performed for adverse events associated with discontinuations. In computing incidence for a given table, a subject reporting more than one episode of the same complaint was counted once at the highest level of severity reported.

8.2 Deaths

There were no deaths in this database.

8.3 Assessment of Dropouts

8.3.1 Overall Pattern of Dropouts

97 (38.5%) of 252 subjects withdrew from treatment during Study 672. The most frequent reasons for discontinuation were adverse event (9.5%, 24/252), lost to follow-up (9.5%, 24/252), other (8.7%, 22/252), and withdrew consent (5.6%, 14/252). In the group that received sertraline in the feeder studies, the most frequent reasons for discontinuation in Study 672 were lost to follow-up (12.5%, 16/128), adverse event (8.6%, 11/128), other (7.0%, 9/128), and withdrew consent (4.7%, 6/128); in the group that received placebo, the most frequent reasons were adverse event (10.5%, 13/124), other (10.5%, 13/124), lost to follow-up (6.5%, 8/124), and withdrew consent (6.5%, 8/124). The 97 subjects who were discontinued for any reason are listed in appendix Table 4.2. Twenty-seven subjects were discontinued for medical reasons: adverse events, 24; abnormal clinical laboratory test results, 2; other, 1.

As shown in Appendix Table 4.1, 48 of 96 subjects withdrew from treatment during study 703. The discontinuation rates for the sertraline and placebo groups were 39% (18/46) and 60% (30/50), respectively. The most frequent reason for discontinuation in the sertraline group was insufficient clinical response (11% [5/46] of sertraline subjects vs. 20% [10/50] of placebo subjects). In the placebo group, the most common reason for discontinuation was that subjects met relapse criteria (28% [14/50] of placebo subjects vs. 7% [3/46] of sertraline subjects). Adverse events led to discontinuation in 9% [4/46] of sertraline subjects vs. 6% [3/50] of placebo subjects.

8.3.2 Adverse Events Associated with Dropout

No subjects were discontinued because of abnormal laboratory values occurring after baseline in Study 672 and there were no

discontinuations for abnormal laboratory values at anytime in Study 703. No subject in either Study 672 or Study 703 discontinued due to any clinically significant vital sign or ECG abnormality. Two subjects, one in each study, were discontinued because of weight gain. The subject discontinued from Study 672 had a clinically significant weight gain. Four sertraline subjects (Appendix Table 4.2.1) and 3 placebo subjects (Table 4.2.2) discontinued from the study due to adverse events (none due to laboratory abnormalities). The adverse events associated with discontinuation and proportions of sertraline and placebo subjects discontinued because of those adverse events are shown in Appendix Table 6.3. There was no significant difference (p= 0.707) overall between the sertraline and placebo groups for the number of subjects who discontinued.

8.4 Search for Serious Adverse Events

Seven serious adverse events were reported in five subjects in Study 672 and two serious adverse events were reported in Study 703. See appendix table 6.1. One of the serious adverse events reported in Study 703 was a fetal death. There is no new pattern evident in these events. The fetal death is described by the sponsor below:

Subject 96N0192/1049, a 32-year-old female, stopped taking sertraline 11 days after her 32nd birthday and 29 days after beginning therapy in Study 703, having learned she was pregnant, despite using barrier contraception. Her final study visit took place 24 days after she stopped study medication. Her final dosage was 100 mg/day. One week later, a sonogram revealed fetal death and the subject underwent a procedure to evacuate the uterus. The cause of fetal death is unknown but not considered treatment-related by the investigator. The subject used erythromycin cream 2% for acne from 1992 until she learned she was pregnant. She also used guaifenesin for serous otitis media at 2400 mg/day during the first 7 days of study treatment and then at 1200 mg/day during 5 additional treatment days. Three days after stopping study drug, she used a fluticasone inhaler for 5 days at 4 puffs/day. In Study 672, she received sertraline at 100 mg/day during her last 159 (of 168) days.

8.5 Other Safety Findings

8.5.1 ADR Incidence Tables

8.5.1.1 Appropriateness of Adverse Event Categorization and Preferred Terms

Adverse event tables are organized according to body system and the preferred adverse event terms are used as listed in the Pfizer World Health Organization (WHO) Adverse Event Coding Glossary. I have reviewed this list and find the organization to be reasonable.

8.5.1.2 Incidence in Controlled Clinical Trials

IN study 703 the predominant (>10% incidence) treatment-emergent adverse events in the sertraline-treated group versus placebo-treated group in order of frequency were: headache (26%, 12/46 vs. 14%, 7/50), malaise (13%, 6/46 vs. 4%, 2/50), insomnia (13%, 6/46 vs. 10%, 5/50), and infection (13%, 6/46 vs. 2% 1/50). The predominant (10% incidence) treatment-emergent adverse events in the placebo-treated group versus sertraline-treated group in order of frequency were: dizziness (22%, 11/50 vs. 7%, 3/46), upper respiratory tract infection (14%, 7/50 vs. 9%, 4/46), nervousness (12%, 6/50 vs. 2%, 1/46), emotional lability (10%, 5/50 vs.4%, 2/46) and diarrhea (10%, 5/50 vs. 4%, 2/46). For dizziness, there was a significantly (p =0.043) greater incidence in the placebo group than in the sertraline group. There was no significant difference between treatment groups for any other adverse event.

8.5.1.3 Post Marketing Spontaneous Reports

There are no post marketing reports relevant to this supplement.

8.5.2 Laboratory Findings

There were no discontinuations due to clinical laboratory abnormalities occurring after baseline evaluation.

The incidence of clinically significant laboratory abnormalities and changes in clinical laboratory test results from baseline to endpoint (last available measurement) were summarized. Laboratory evaluations made up to 7 days after the last dose of study drug were included in these analyses. The incidence rates of subjects with clinically significant laboratory abnormalities (by laboratory parameter) were compared between treatment groups using Fisher's

exact test. Mean changes in clinical laboratory test results from baseline of Study 703 to endpoint of Study 703 were summarized by treatment group; comparisons between treatment groups were performed using the Wilcoxon rank sum test.

The criteria used in this study for clinically significant laboratory abnormalities were identical to those used for adults in sertraline Safety Update II for NDA #19-839 submitted on October 30, 1991.

8.5.2.1 Clinical Chemistry Findings

The incidence of clinically significant laboratory test abnormalities and the criteria for determining such abnormalities are shown in appendix Table 7.1.1.

Appendix table 7.2 compares mean changes from baseline to endpoint in laboratory test values between the sertraline and placebo treatment groups. There was no statistically significant difference ($p > 0.05$) between treatment groups for any laboratory test result.

There were no discontinuations due to clinical laboratory abnormalities occurring after baseline evaluation.

8.5.2.2 Hematology Findings

Appendix table 7.2 compares mean changes from baseline to endpoint in laboratory test values between the sertraline and placebo treatment groups. There was no statistically significant difference ($p > 0.05$) between treatment groups for any hematology test result.
There were no discontinuations due to hematology laboratory abnormalities occurring after baseline evaluation.

8.5.2.3 Urinalysis

Appendix table 7.2 compares mean changes from baseline to endpoint in laboratory test values between the sertraline and placebo treatment groups. There was no statistically significant difference ($p > 0.05$) between treatment groups for any laboratory test result.
Only one placebo patient had a minor urinary abnormality.

There were no discontinuations due to clinical laboratory abnormalities occurring after baseline evaluation.

8.5.3 Vital Signs

Three (7%) of 44 sertraline subjects and 1 (2%) of 50 placebo subjects had clinically significant vital sign abnormalities in Study 703. There was no statistically significant difference between treatment groups mean changes from baseline in vital signs ($p > 0.05$). No subjects discontinued due to changes in vital signs.

7% of 44 subjects in the sertraline group and 8% of 50 subjects in the placebo group experienced a clinically significant weight increase >(7%)from baseline of Study 703. No subject had a mean decrease in body weight > 7%. The sertraline and placebo groups had mean increases in body weight of 3.34 lb. (baseline: 181.1 lb.) and 1.57 lb. (baseline: 168.7 lb.), respectively; the difference was not statistically significant ($p = 0.1162$). One sertraline-treated subject (No. 96N0199/1123) was discontinued due to a mild body weight increase that was attributed to study drug. See appendix lab tables.

8.5.4 ECGs

There were no clinically significant ECG abnormalities during the study in any subject. There was no statistically significant difference between treatment groups in the incidence of ECG changes from normal to a non-clinically significant abnormality ($p = 1.000$): 12% (4/34) and 9% (3/35) in the sertraline-treated and placebo-treated groups, respectively. No subject discontinued because of ECG abnormalities. See appendix lab tables.

8.5.5 Special Studies

None.

8.5.6 Withdrawal Phenomena/Abuse Potential

No new information.

8.5.7 Human Reproduction Data

No new information.

8.6 Overdose Experience

No new information.

8.7 Summary of Important Events Considered Drug Related

There is no new pattern of drug related events for this submission.

8.8 Important Events Considered Not Drug Related

Certain events have been discussed elsewhere in this document and have been excluded from this list (i.e., deaths, overdoses, dropouts and changes in laboratory values).

The rest of the serious adverse events are considered not drug related and they are displayed in the Appendix of serious adverse events.

8.9 Summary of Drug Interactions

8.9.1 Drug-Demographic Interactions

GENDER:

There is no significant interaction by gender reported.

AGE:

There is no significant interaction by age reported.

RACE:

There is no significant interaction by race reported.

8.9.2 Drug-Disease Interactions

There are no new drug-disease interactions reported.

8.9.3 Drug-Drug Interactions

There are no new drug-drug interactions reported.

9.0 Labeling Review

The following has been added to the clinical trials section.

Study 5 demonstrated the efficacy of ZOLOFT in the long-term treatment of PTSD for up to 52 weeks. Patients who had completed 12 weeks of double-blind placebo-controlled treatment entered Study 5 and were then treated with open-label ZOLOFT for 24 weeks in the dose-range of 50-200 mg/day. Responders were randomized (N=96) to an additional 28 weeks of double-blind ZOLOFT or placebo treatment. Patients randomized to ZOLOFT had a significantly lower rate of discontinuation due to relapse or insufficient clinical response than did patients randomized to placebo. This pattern was demonstrated in both male and female subjects. There was insufficient information to determine the effect of race or age on outcome.

The following has been added to the indication section.

The efficacy of ZOLOFT in the long-term treatment of PTSD was demonstrated for up to 52 weeks, in a design which consisted of 24 weeks open-label treatment followed by 28 weeks of placebo-controlled double-blind treatment. In the final phase of treatment, patients randomized to ZOLOFT had a significantly lower rate of discontinuation due to relapse or insufficient clinical response than did patients randomized to placebo. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

The following has been added to

8.9.2 Drug-Disease Interactions

There are no new drug-disease interactions reported.

8.9.3 Drug-Drug Interactions

There are no new drug-drug interactions reported.

9.0 Labeling Review

The following has been added to the clinical trials section.

Study 5 demonstrated the efficacy of ZOLOFT in the long-term treatment of PTSD for up to 52 weeks. Patients who had completed 12 weeks of double-blind placebo-controlled treatment entered Study 5 and were then treated with open-label ZOLOFT for 24 weeks in the dose-range of 50-200 mg/day. Responders were randomized (N=96) to an additional 28 weeks of double-blind ZOLOFT or placebo treatment. Patients randomized to ZOLOFT had a significantly lower rate of discontinuation due to relapse or insufficient clinical response than did patients randomized to placebo. This pattern was demonstrated in both male and female subjects. There was insufficient information to determine the effect of race or age on outcome.

The following has been added to the indication section.

The efficacy of ZOLOFT in the long-term treatment of PTSD was demonstrated for up to 52 weeks, in a design which consisted of 24 weeks open-label treatment followed by 28 weeks of placebo-controlled double-blind treatment. In the final phase of treatment, patients randomized to ZOLOFT had a significantly lower rate of discontinuation due to relapse or insufficient clinical response than did patients randomized to placebo. The usefulness of the drug in patients receiving ZOLOFT for extended periods should be reevaluated periodically (see Clinical Trials under CLINICAL PHARMACOLOGY).

The following has been added to

Maintenance/Continuation/Extended Treatment

[redacted]

Dosage adjustments may be needed to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

[redacted]

Under PTSD clinical trials I would change the last sentence to "There was insufficient information to determine the effect of race, gender or age on outcome." I think this would help to reemphasize that the gender discrepancy in the initial studies has not yet been resolved.

The change in the Indications section is acceptable.

The change in the Dosage and Administration section is acceptable.

The change in the Maintenance/Continuation/Extended Treatment section is acceptable.

10.0 Conclusions

The results of study 703 demonstrate that sertraline is significantly more effective than placebo in preventing worsening of PTSD symptoms as evidenced by relapse, relapse/discontinuation due to insufficient clinical response, and acute exacerbation of PTSD. The statistical reviewer John Lawrence Ph.D. agrees with this conclusion. Safety was comparable between the two treatment groups.

11.0 Recommendations

I recommend we approve this supplement and that the labeling suggested by the sponsor be accepted with the changes noted in the labeling section.

Earl D. Hearst, M.D.
Medical Reviewer

INDEX

PROTOCOL: 96-121 0705
STUDY: A DOUBLE BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST TRAUMATIC [illegible] DISORDER

TABLE 2.1: SUMMARY OF SUBJECT DEMOGRAPHICS AND CHARACTERISTICS BY TREATMENT GROUP - ALL RANDOMIZED SUBJECTS

		SERTRALINE	PLACEBO	P-VALUE (1)
Sex:	Female	36	31	
	Male	10	15	
	Total	46	46	0.304
Race:	Asian	2	2	
	Black	4	0	
	White	40	38	
	Other	0	6	0.145
Age (yrs): (2)	N	46	46	
	Mean	44.9	42.0	0.161
	Std. Dev.	9.8	10.4	
	Minimum	24.0	21.0	
	Maximum	68.0	63.0	
Weight (lbs): (2)	N	46	46	
	Mean	174.1	168.2	0.249
	Std. Dev.	41.3	36.2	
	Minimum	105.6	97.0	
	Maximum	292.0	268.0	
Duration of Illness (yrs): (3)	N	46	46	
	Mean	12.2	13.4	0.520
	Std. Dev.	13.0	12.8	
	Minimum	0.6	0.7	
	Maximum	58.8	54.0	
Time from Traumatic Event (yrs): (3)	N	46	46	
	Mean	14.5	15.7	0.966
	Std. Dev.	14.7	15.1	
	Minimum	0.8	0.7	
	Maximum	57.8	53.4	
Comorbid Axis I Diagnosis: (3) (4)	Anxiety	10	9	
	Depression	16	22	
	Dysthymia	3	1	
	None	29	21	
	Other	1	1	

(1) P-values for sex and race were determined using the Chi-square and Fisher exact test respectively, with non-white races pooled for race comparisons. P-value for age, weight, time from traumatic event and duration of illness were based on F-test from two-way ANOVA (treatment and site as effects).
(2) Reported at study 705 baseline.
(3) Reported at the feeder study (study 671 or 682) baseline.
(4) Subject may have had more than one diagnosis.

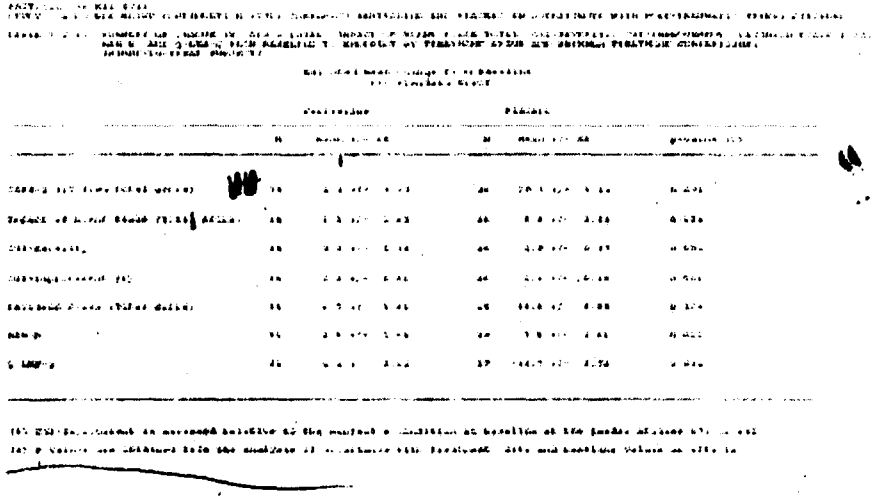
PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

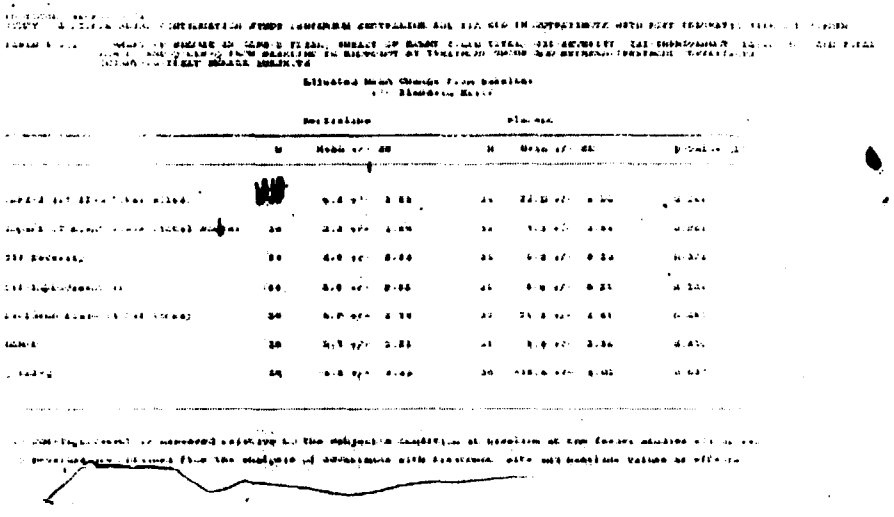
TABLE 5.1.1: SUMMARY OF CAPS-2 TOTAL, IMPACT OF EVENT SCALE TOTAL, CGI-SEVERITY, CGI-IMPROVEMENT, DAVIDSON SCALE TOTAL, HAM-D, AND Q-LES-Q AT BASELINE BY TREATMENT GROUP AND BETWEEN-TREATMENT COMPARISONS:
INTENT-TO-TREAT SUBJECTS

	Sertraline		Placebo		
	N	Mean +/- SD	N	Mean +/- SD	p-value (2)
CAPS-2 (17 Item total score)	38	14.8 +/- 11.3	46	16.1 +/- 11.4	0.904
Impact of Event Scale (Total score)	38	6.5 +/- 6.8	46	7.4 +/- 8.5	0.706
CGI-Severity	38	2.1 +/- 0.9	46	2.2 +/- 0.9	0.912
CGI-Improvement (1)	38	1.4 +/- 0.5	46	1.4 +/- 0.5	0.955
Davidson Scale (Total Score)	38	15.9 +/- 13.7	45	17.6 +/- 14.6	0.894
HAM-D	33	5.2 +/- 3.4	39	6.9 +/- 4.9	0.222
Q-LES-Q	33	75.4 +/- 12.6	37	76.6 +/- 10.9	0.743

(1) CGI-Improvement is assessed relative to the subject's condition at baseline at the feeder studies 671 or 682.

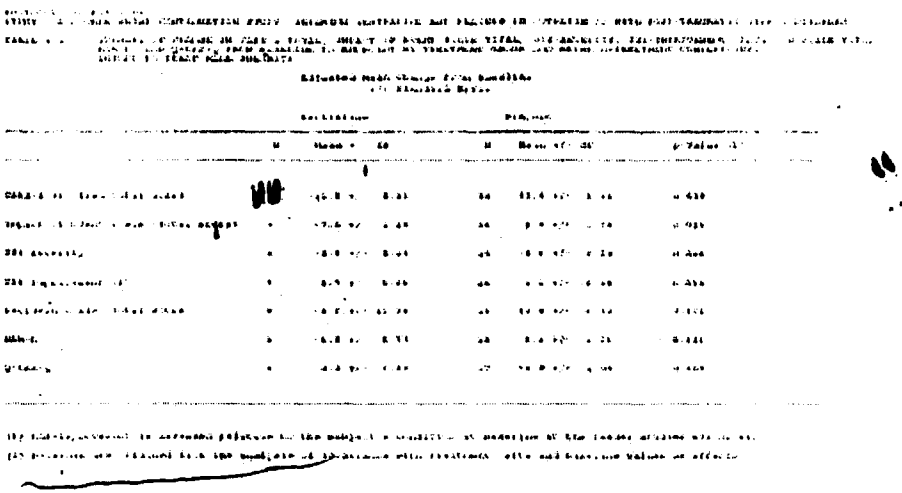
(2) P-values were based on F-test from two-way ANOVA (treatment and site as effects).





Estimated Mean Change from Baseline
in Bladder Mass

	Ranitidine			Placebo		
	N	Mean +/- SE		N	Mean +/- SE	
[illegible]	[illegible]	9.6 +/- 3.55		24	22.0 +/- 4.04	
[illegible]	30	2.6 +/- 3.55		34	9.3 +/- 4.04	
210 Decrease,	30	6.0 +/- 3.55		34	9.0 +/- 4.04	
[illegible]	100	5.0 +/- 3.55		45	9.0 +/- 4.04	
[illegible]	30	5.0 +/- 3.55		34	9.0 +/- 4.04	
[illegible]	30	5.0 +/- 3.55		34	9.0 +/- 4.04	
[illegible]	30	5.0 +/- 3.55		34	9.0 +/- 4.04	



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PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 5.5.1: NUMBER AND PERCENT OF RESPONDERS(1) AT EACH VISIT BY GENDER AND TREATMENT GROUP: INTENT-TO-TREAT SUBJECTS
NUMBER OF RESPONDERS/TOTAL NUMBER OF SUBJECTS (%)

	TOTAL		FEMALE		MALE	
VISIT WEEK	SERTRALINE	PLACEBO	SERTRALINE	PLACEBO	SERTRALINE	PLACEBO
WEEK 2	34/38 (89.5)	25/46 (54.3)	25/29 (86.2)	16/28 (57.1)	9/ 9 (100.0)	9/18 (50.0)
WEEK 4	32/37 (86.5)	23/38 (60.5)	23/28 (82.1)	12/21 (57.1)	9/ 9 (100.0)	11/17 (64.7)
WEEK 6	31/32 (96.9)	21/29 (72.4)	23/24 (95.8)	11/16 (68.8)	8/ 8 (100.0)	10/13 (76.9)
WEEK 8	30/32 (93.8)	19/24 (79.2)	21/23 (91.3)	10/13 (76.9)	9/ 9 (100.0)	9/11 (81.8)
WEEK 10	29/30 (96.7)	16/19 (84.2)	21/22 (95.5)	8/10 (80.0)	8/ 8 (100.0)	8/ 9 (88.9)
WEEK 12	28/30 (93.3)	16/20 (80.0)	20/21 (95.2)	9/11 (81.8)	8/ 9 (88.9)	7/ 9 (77.8)
WEEK 14	25/26 (96.2)	17/19 (89.5)	18/19 (94.7)	10/11 (90.9)	7/ 7 (100.0)	7/ 8 (87.5)
WEEK 16	24/25 (96.0)	17/19 (89.5)	18/19 (94.7)	9/10 (90.0)	6/ 6 (100.0)	8/ 9 (88.9)
WEEK 18	24/25 (96.0)	17/19 (89.5)	18/19 (94.7)	10/10 (100.0)	6/ 6 (100.0)	7/ 9 (77.8)
WEEK 20	25/25 (100.0)	17/17 (100.0)	18/18 (100.0)	9/ 9 (100.0)	7/ 7 (100.0)	8/ 8 (100.0)
WEEK 22	25/25 (100.0)	18/19 (94.7)	18/18 (100.0)	10/10 (100.0)	7/ 7 (100.0)	8/ 9 (88.9)
WEEK 24	23/24 (95.8)	18/19 (94.7)	17/18 (94.4)	10/10 (100.0)	6/ 6 (100.0)	8/ 9 (88.9)
WEEK 26	25/25 (100.0)	16/18 (88.9)	18/18 (100.0)	10/10 (100.0)	7/ 7 (100.0)	6/ 8 (75.0)
WEEK 28	24/24 (100.0)	17/18 (94.4)	17/17 (100.0)	8/ 9 (88.9)	7/ 7 (100.0)	9/ 9 (100.0)

1) RESPONDERS ARE SUBJECTS WITH AT LEAST 30% DECREASE IN CAPS-2 TOTAL (AS COMPARED TO BASELINE OF THE FEEDER STUDIES 671 OR 682) AND A CGI IMPROVEMENT = 1 OR 2

PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 5.5.2: RATES OF RESPONSE(1) AT ENDPOINT AND AT ANY TIME DURING THE STUDY AND BETWEEN-TREATMENT COMPARISONS: INTENT-TO-TREAT SUBJECTS

	SERTRALINE	PLACEBO	ODDS RATIO (95% CI)(2)	P-VALUE(3)
TOTAL NUMBER OF SUBJECTS	38	46		
NO. (%) OF RESPONDERS AT ENDPOINT	30 (78.9)	21 (45.7)	4.464 (1.689-11.800)	0.0032
NO. (%) OF RESPONDERS AT ANY TIME DURING THE STUDY	36 (94.7)	30 (65.2)	9.600 (2.042-45.129)	0.0011

(1) RESPONDERS ARE SUBJECTS WITH AT LEAST 30% DECREASE IN CAPS-2 TOTAL (AS COMPARED TO BASELINE OF THE FEEDER STUDIES 671 OR 682) AND A CGI IMPROVEMENT = 1 OR 2
(2) THE ODDS RATIO IS THE RATIO OF THE ODDS OF EVENT IN SERTRALINE GROUP RELATIVE TO THE PLACEBO GROUP
(3) P-VALUE BASED ON FISHER'S EXACT TEST

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TABLE 5.6.1: SUMMARY OF TIME TO RELAPSE(1) ANALYSIS:
INTENT-TO-TREAT SUBJECTS

	SERTRALINE				PLACEBO		
WEEK (DAYS)(2)	N ENTERED WEEK	N RELAPSED DURING WEEK	N CENSORED(3) DURING WEEK	S(t)(4)	N ENTERED WEEK	N RELAPSED DURING WEEK	N CENSORED(3) DURING WEEK S(t)(4)
1 (1- 7)	38	0	0	1.0000	46	1	1
0.9783							
2 (8- 14)	38	2	0	0.9474	44	6	3
0.8449							
3 (15- 21)	36	0	0	0.9474	35	2	3
0.7966							
4 (22- 28)	36	0	2	0.9474	30	0	1
0.7966							
5 (29- 35)	34	0	1	0.9474	29	0	0
0.7966							
6 (36- 42)	33	0	1	0.9474	29	1	4
0.7691							
7 (43- 49)	32	0	0	0.9474	24	0	1
0.7691							
8 (50- 56)	32	0	0	0.9474	23	1	1
0.7357							
9 (57- 63)	32	0	1	0.9474	21	0	1
0.7357							

10 (64- 70)	31	0	1	0. 9474	20	0	0
0. 7357							
11 (71- 77)	30	0	0	0. 9474	20	0	0
0. 7357							
12 (78- 84)	30	0	0	0. 9474	20	1	0
0. 6989							
13 (85- 91)	30	0	1	0. 9474	19	0	0
0. 6989							
14 (92- 98)	29	0	1	0. 9474	19	0	0
0. 6989							
15 (99-105)	28	0	1	0. 9474	19	0	0
0. 6989							
16 (106-112)	27	0	1	0. 9474	19	0	0
0, 6989							
17 (113-119)	26	0	0	0. 9474	19	0	0
0. 6989							
18 (120-126)	26	0	0	0. 9474	19	0	0
0. 6989							
19 (127-133)	26	0	0	0. 9474	19	0	0
0. 6989							
20 (134-140)	26	0	1	0. 9474	19	0	0
0. 6989							
21 (141-147)	25	0	0	0. 9474	19	0	0
0. 6989							
22 (148-154)	25	0	0	0. 9474	19	0	0
0. 6989							
23 (155-161)	25	0	0	0. 9474	19	0	0
0. 6989							
24 (162-168)	25	0	0	0. 9474	19	0	0
0. 6989							
25 (169-175)	25	0	0	0. 9474	19	0	0
0. 6989							

26 (176-182)	25	0	0	0.9474	19	0	0
0.6989							
27 (183-189)	25	0	0	0.9474	19	0	0
0.6989							
28 (>=190)	25	0	1	0.9474	19	0	0
0.6989							

LOG-RANK TEST P-VALUE: 0.0070

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(1) TIME TO RELAPSE IS THE TIME TO THE FIRST OF TWO CONSECUTIVE VISITS THAT MEET RELAPSE CRITERIA.
(2) WEEK REPRESENTS 7 CALENDAR DAYS.
(3) CENSORED DENOTES A SUBJECT WHO DISCONTINUED THE STUDY FOR REASONS OTHER THAN RELAPSE.
(4) S(t) IS THE KAPLAN-MEIER ESTIMATE OF THE PROBABILITY TO BE RELAPSE-FREE (SURVIVAL PROBABILITY).

PROTOCOL: 96CE21-0703

STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 5.6.2: SUMMARY OF TIME TO DISCONTINUATION(1) DUE TO RELAPSE OR INSUFFICIENT CLINICAL RESPONSE ANALYSIS: INTENT-TO-TREAT SUBJECTS

	SERTRALINE				PLACEBO			
WEEK (DAYS)(2)	N ENTERED WEEK	N DISCONT. DURING WEEK	N CENSORED(3) DURING WEEK	S(t)(4)	N ENTERED WEEK	N DISCONT. DURING WEEK	N CENSORED(3) DURING WEEK	S(t)(4)
1 (1- 7)	38	0	0	1.0000	46	1	1	0.9783
2 (8- 14)	38	2	0	0.9474	44	9	0	0.7782
3 (15- 21)	36	0	0	0.9474	35	3	2	0.7115
4 (22- 28)	36	0	2	0.9474	30	1	0	0.6877
5 (29- 35)	34	0	1	0.9474	29	0	0	0.6877
6 (36- 42)	33	0	1	0.9474	29	3	2	0.6166
7 (43- 49)	32	0	0	0.9474	24	1	0	0.5909
8 (50- 56)	32	0	0	0.9474	23	2	0	0.5395
9 (57- 63)	32	1	0	0.9178	21	0	1	0.5395
10 (64- 70)	31	0	1	0.9178	20	0	0	0.5395
11 (71- 77)	30	0	0	0.9178	20	0	0	0.5395
12 (78- 84)	30	0	0	0.9178	20	1	0	0.5125
13 (85- 91)	30	0	1	0.9178	19	0	0	0.5125
14 (92- 98)	29	0	1	0.9178	19	0	0	0.5125
15 (99-105)	28	1	0	0.8850	19	0	0	0.5125
16 (106-112)	27	1	0	0.8522	19	0	0	0.5125
17 (113-119)	26	0	0	0.8522	19	0	0	0.5125
18 (120-126)	26	0	0	0.8522	19	0	0	0.5125
19 (127-133)	26	0	0	0.8522	19	0	0	0.5125
20 (134-140)	26	1	0	0.8194	19	0	0	0.5125
21 (141-147)	25	0	0	0.8194	19	0	0	0.5125
22 (148-154)	25	0	0	0.8194	19	0	0	0.5125
23 (155-161)	25	0	0	0.8194	19	0	0	0.5125
24 (162-168)	25	0	0	0.8194	19	0	0	0.5125
25 (169-175)	25	0	0	0.8194	19	0	0	0.5125
26 (176-182)	25	0	0	0.8194	19	0	0	0.5125
27 (183-189)	25	0	0	0.8194	19	0	0	0.5125
28 (>=190)	25	0	1	0.8194	19	0	0	0.5125

LOG-RANK TEST P-VALUE: 0.0016

(1) TIME TO DISCONTINUATION IS THE TIME TO THE VISIT WHEN SUBJECT MET RELAPSE CRITERIA FOR THE FIRST TIME OR DISCONTINUED THE STUDY DUE TO INSUFFICIENT CLINICAL RESPONSE.

(2) WEEK REPRESENTS 7 CALENDAR DAYS.

(3) CENSORED DENOTES A SUBJECT WHO DISCONTINUED THE STUDY FOR REASONS OTHER THAN RELAPSE/INSUFFICIENT RESPONSE.

(4) S(t) IS THE KAPLAN-MEIER ESTIMATE OF THE PROBABILITY NOT TO DISCONTINUE DUE TO RELAPSE OR INSUFFICIENT CLINICAL RESPONSE (SURVIVAL PROBABILITY).

PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 5.6.3: SUMMARY OF TIME TO THE FIRST ACUTE EXACERBATION OF PTSD(1) ANALYSIS:
INTENT-TO-TREAT SUBJECTS

	SERTRALINE				PLACEBO			
WEEK (DAYS)(2)	N ENTERED WEEK	N ACUTE EX. DURING WEEK	N CENSORED(3) DURING WEEK	S(t)(4)	N ENTERED WEEK	N ACUTE EX. DURING WEEK	N CENSORED(3) DURING WEEK	S(t)(4)
1 (1- 7)	38	0	0	1.0000	46	2	0	0.9565
2 (8- 14)	38	2	0	0.9474	44	9	0	0.7609
3 (15- 21)	36	0	0	0.9474	35	3	2	0.6957
4 (22- 28)	36	0	2	0.9474	30	1	0	0.6725
5 (29- 35)	34	0	1	0.9474	29	0	0	0.6725
6 (36- 42)	33	0	1	0.9474	29	3	2	0.6029
7 (43- 49)	32	0	0	0.9474	24	1	0	0.5778
8 (50- 56)	32	0	0	0.9474	23	2	0	0.5275
9 (57- 63)	32	1	0	0.9178	21	1	0	0.5024
10 (64- 70)	31	0	1	0.9178	20	0	0	0.5024
11 (71- 77)	30	0	0	0.9178	20	0	0	0.5024
12 (78- 84)	30	0	0	0.9178	20	1	0	0.4773
13 (85- 91)	30	0	1	0.9178	19	0	0	0.4773
14 (92- 98)	29	0	1	0.9178	19	0	0	0.4773
15 (99-105)	28	1	0	0.8850	19	0	0	0.4773
16 (106-112)	27	1	0	0.8522	19	0	0	0.4773
17 (113-119)	26	0	0	0.8522	19	0	0	0.4773
18 (120-126)	26	0	0	0.8522	19	0	0	0.4773
19 (127-133)	26	0	0	0.8522	19	0	0	0.4773
20 (134-140)	26	1	0	0.8194	19	0	0	0.4773
21 (141-147)	25	0	0	0.8194	19	0	0	0.4773
22 (148-154)	25	0	0	0.8194	19	0	0	0.4773
23 (155-161)	25	0	0	0.8194	19	0	0	0.4773
24 (162-168)	25	0	0	0.8194	19	0	0	0.4773
25 (169-175)	25	0	0	0.8194	19	0	0	0.4773
26 (176-182)	25	0	0	0.8194	19	0	0	0.4773
27 (183-189)	25	0	0	0.8194	19	0	0	0.4773
28 (>=190)	25	0	1	0.8194	19	1	0	0.4522

LOG-RANK TEST P-VALUE: 0.0003

(1) TIME TO ACUTE EXACERBATION IS THE TIME TO THE VISIT WHEN SUBJECT MET ACUTE EXACERBATION CRITERIA.
(2) WEEK REPRESENTS 7 CALENDAR DAYS.

(3) CENSORED DENOTES A SUBJECT WHO DISCONTINUED THE STUDY FOR REASONS OTHER THAN RELAPSE/INSUFFICIENT RESPONSE/ACUTE EXACERBATION
(4) S(t) IS THE KAPLAN-MEIER ESTIMATE OF THE PROBABILITY NOT TO EXPERIENCE ACUTE EXACERBATION OF PTSD (SURVIVAL PROBABILITY).

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PROTOCOL: 9GCE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 5.7.1: PROPORTION OF SUBJECTS WITH RELAPSE, RELAPSE/INSUFFICIENT CLINICAL RESPONSE AND ACUTE EXACERBATION OF PTSD BY TREATMENT GROUP AND BETWEEN-TREATMENT COMPARISONS: INTENT-TO-TREAT SUBJECTS

	SERTRALINE	PLACEBO	ODDS RATIO (95% CI)(1)	P-VALUE(2)
TOTAL NUMBER OF SUBJECTS	38	46		
NO. (%) OF SUBJECTS WITH RELAPSE	2 (5.3)	12 (26.1)	6.353 (1.324-30.494)	0.0166
NO. (%) OF SUBJECTS WITH RELAPSE OR INSUFFICIENT CLINICAL RESPONSE	6 (15.8)	21 (45.7)	4.480 (1.572-12.768)	0.0047
NO. (%) OF SUBJECTS WITH ACUTE EXACERBATION OF PTSD	6 (15.8)	24 (52.2)	5.818 (2.043-16.567)	0.0006

(1) THE ODDS RATIO IS THE RATIO OF THE ODDS OF EVENT IN PLACEBO GROUP RELATIVE TO THE SERTRALINE GROUP
(2) P-VALUE BASED ON FISHER'S EXACT TEST

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PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 5.7.2: PROPORTION OF SUBJECTS WITH RELAPSE, RELAPSE/INSUFFICIENT CLINICAL RESPONSE, AND ACUTE EXACERBATION OF PTSD BY GENDER AND TREATMENT GROUP: INTENT-TO-TREAT SUBJECTS

	FEMALES		MALES	
	SERTRALINE	PLACEBO	SERTRALINE	PLACEBO
TOTAL NUMBER OF SUBJECTS	29	28	9	18
NO. (%) OF SUBJECTS WITH RELAPSE	2 (6.9)	7 (25.0)	0 (0.0)	5 (27.8)
NO. (%) OF SUBJECTS WITH RELAPSE OR INSUFFICIENT CLINICAL RESPONSE	5 (17.2)	13 (46.4)	1 (11.1)	8 (44.4)
NO. (%) OF SUBJECTS WITH ACUTE EXACERBATION OF PTSD	5 (17.2)	15 (53.6)	1 (11.1)	9 (50.0)

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Figure 1. Kaplan-Meier Estimate of Cumulative Survival Probabilities (Probabilities to be Relapse-free)

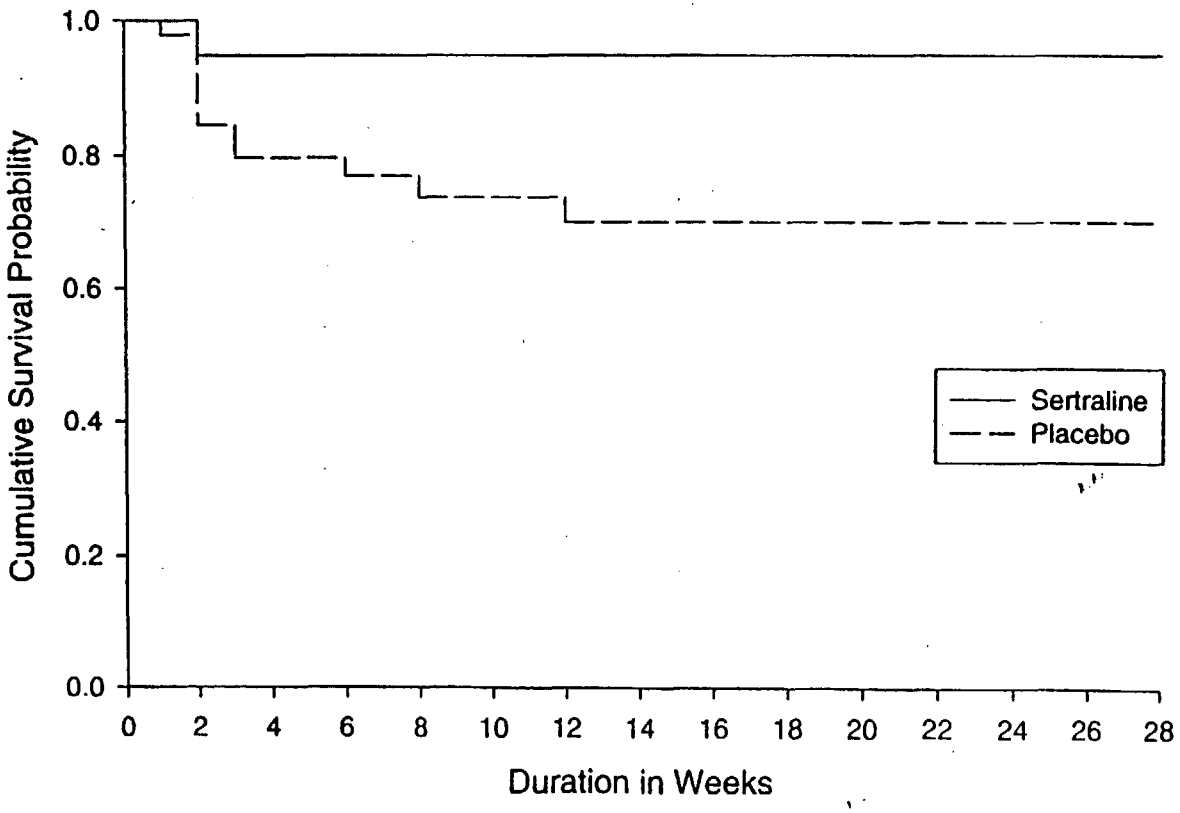
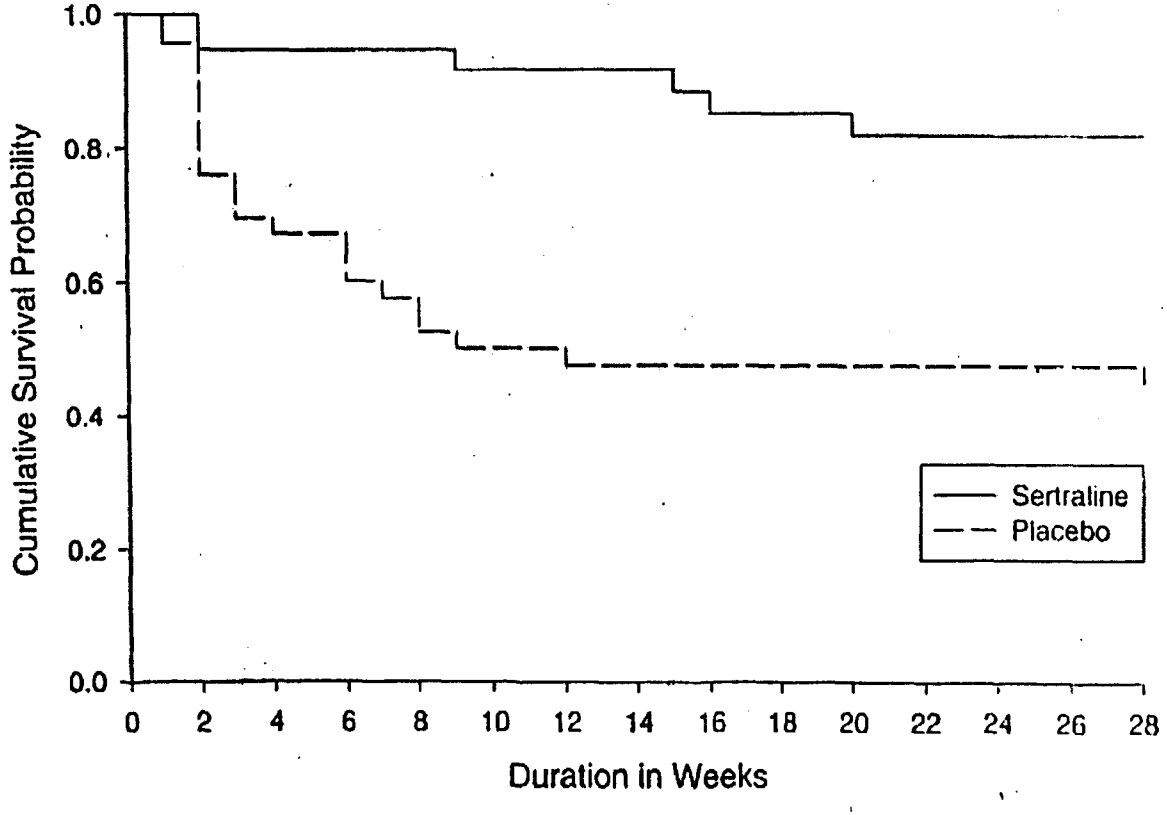


Figure 3. Kaplan-Meier Estimate of Cumulative Survival Probabilities (Probabilities to be Acute Exacerbation-free)



PROTOCOL: 96CE21-0703

A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

APPENDIX I.A: SUBJECTS WHO DISCONTINUED DUE TO MEDICAL REASONS

(1) SERTRALINE TREATMENT GROUP

SITE NO.	SUBJECT NO.	SEX	AGE (years)	DOSE AT DISCONTINUATION (mg/day)	DURATION OF THERAPY (days)[a]	REASON FOR DISCONTINUATION	COMMENTS
96N0186	1030	Male	49	100	91	Adverse Event	Severe chest pain that was attributed to atherosclerotic disease. Resolved on day of event, 1 day before final dose.
96N0192	1049	Female	32	100	29	Other—Pregnancy	Unplanned pregnancy despite barrier contraception. Previously received 159 days of 100 mg/day sertraline open-label treatment in Study 672. Subject discontinued treatment upon knowledge of pregnancy (11 days after her 32nd birthday). One month later, a sonogram revealed fetal death.[b] The cause of fetal death was unknown but not considered treatment-related. The subject used erythromycin cream 2% for acne from 1992 until she learned she was pregnant. She also used guaifenesin for serous otitis media at 2400 mg/day during the first 7 days of study treatment and then at 1200 mg/day during 5 additional treatment days. Three days after stopping study drug, she used a fluticasone inhaler for 5 days at 4 puffs/day.
96N0194	1064	Female	47	150	4	Adverse Event	Mild insomnia and palpitation that were attributed to study drug. Resolved 3 days after final dose.
96N0198	1101	Female	46	150	65	Adverse Event	Moderate depression that was attributed to study drug. Resolved 43 days after final dose.

[a] Duration of treatment in study 703.

[b] Fetal death reported as serious adverse event.

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PROTOCOL: 96CE21-0703

A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

K I.A: SUBJECTS WHO DISCONTINUED DUE TO MEDICAL REASONS

(1) SERTRALINE TREATMENT GROUP

SITE NO.	SUBJECT NO.	SEX	AGE (years)	DOSE AT DISCONTINUATION (mg/day)	DURATION OF THERAPY (days)[a]	REASON FOR DISCONTINUATION	COMMENTS
96N0199	1123	Female	39	25	202	Adverse Event	Mild body weight increase that was attributed to study drug. At the end of Week 10, the subject's weight was 132 lb. It increased to a maximum of 138.5 lb. at the end of Week 24. At her discontinuation at the end of Week 26, her weight was 137 lb. (Her Study 703 baseline weight was 135 lb.). There was no date of resolution.

[a] Duration of treatment in study 703.

[b] Fetal death reported as serious adverse event.

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PROTOCOL: 95CE21-0672
STUDY: A 24-WEEK OPEN-LABEL EXTENSION STUDY OF SERTRALINE IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 4.1: SUMMARY OF ALL DISCONTINUATIONS FROM THE STUDY FOR SAFETY ANALYZABLE SUBJECTS

	ALL SUBJECTS	SERT-SERT (1)	PLAC-SERT (2)
REASON FOR DISCONTINUATION	N (%)	N (%)	N (%)
TOTAL NO. OF SUBJECTS	252	128	124
NO. OF SUBJECTS DISCONTINUED	97 (38.5)	51 (39.8)	46 (37.1)
INSUFFICIENT CLINICAL RESPONSE	5 (2.0)	2 (1.6)	3 (2.4)
ADVERSE EVENT	24 (9.5)	11 (8.6)	13 (10.5)
LABORATORY ABNORMALITY *	2 (0.8)	2 (1.6)	0 (0.0)
SPECIAL SAFETY TEST	0 (0.0)	0 (0.0)	0 (0.0)
SUBJECT DIED	0 (0.0)	0 (0.0)	0 (0.0)
PROTOCOL VIOLATION	6 (2.4)	5 (3.9)	1 (0.8)
LOST TO FOLLOW-UP	24 (9.5)	16 (12.5)	8 (6.5)
DID NOT MEET ENTRANCE CRITERIA	0 (0.0)	0 (0.0)	0 (0.0)
WITHDREW CONSENT	14 (5.6)	6 (4.7)	8 (6.5)
OTHER	22 (8.7)	9 (7.0)	13 (10.5)

(1): SAFETY ANALYZABLE SUBJECTS RANDOMIZED TO SERTRALINE IN THE FEEDER STUDIES
(2): SAFETY ANALYZABLE SUBJECTS RANDOMIZED TO PLACEBO IN THE FEEDER STUDIES
* SUBJECT 7040 (GRANT=95NO091, SEX=MALE) DISCONTINUED THE STUDY DUE TO ADVERSE EVENTS (SGOT INCREASED, SGPT INCREASED) WHICH HAD ONSET PRIOR TO ENTRY INTO STUDY 672. "LABORATORY ABNORMALITY" IS REPORTED AS A REASON FOR DISCONTINUATION

PROTOCOL: [illegible] 0472

[illegible] A [illegible] WEEK OPEN-LABEL EXTENSION STUDY OF SERTRALINE IN OUTPATIENTS WITH POST TRAUMATIC STRESS DISORDER

TABLE [illegible] LISTING OF ALL DISCONTINUATIONS FROM THE STUDY FOR SAFETY ANALYZABLE SUBJECTS

[illegible]	PATIENT	GROUP	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (MG/DAY)	DURATION OF THERAPY (DAYS) (1)	REASON
[illegible]	[illegible]	PLAC-SERT	F	[illegible]	200	50	OTHER
[illegible]	[illegible]	SERT-SERT	F	[illegible]	150	114	ADVERSE EVENT
[illegible]	[illegible]	SERT-SERT	F	[illegible]	200	102	PROTOCOL VIOLATION
[illegible]	[illegible]	PLAC-SERT	F	[illegible]	150	65	ADVERSE EVENT
[illegible]	[illegible]	SERT-SERT	F	[illegible]	200	[illegible]	ADVERSE EVENT
[illegible]	2067	PLAC-SERT	F	[illegible]	150	192	ADVERSE EVENT
[illegible]	1071	SERT-SERT	F	[illegible]	200	160	PROTOCOL VIOLATION
[illegible]	[illegible]	PLAC-SERT	M	[illegible]	25	-	ADVERSE EVENT
[illegible]	[illegible]	PLAC-SERT	F	[illegible]	[illegible]	[illegible]	WITHDREW CONSENT
[illegible]	[illegible]	SERT-SERT	F	[illegible]	200	144	LOST TO FOLLOW-UP
[illegible]	[illegible]	PLAC-SERT	[illegible]	[illegible]	25	[illegible]	WITHDREW CONSENT
[illegible]	[illegible]	PLAC-SERT	[illegible]	[illegible]	[illegible]	[illegible]	WITHDREW CONSENT
[illegible]	[illegible]	PLAC-SERT	F	[illegible]	200	[illegible]	WITHDREW CONSENT
[illegible]	[illegible]	PLAC-SERT	F	[illegible]	200	[illegible]	ADVERSE EVENT
[illegible]	[illegible]	SERT-SERT	F	[illegible]	200	[illegible]	ADVERSE EVENT

-(CONTINUED)-

(1) DURATION IS CALCULATED FROM THE START OF THERAPY IN STUDY 472

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PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER
TABLE 4.1: SUMMARY OF DISCONTINUATIONS FROM THE STUDY BY TREATMENT GROUP FOR SAFETY ANALYZABLE SUBJECTS

	NUMBER OF SUBJECTS	
REASON FOR DISCONTINUATION	SERTRALINE N (%)	PLACEBO N (%)
TOTAL NO. OF SUBJECTS	46	50
NO. OF SUBJECTS DISCONTINUED	18 (39.1)	30 (60.0)
MET RELAPSE CRITERIA	3 (6.5)	14 (28.0)
INSUFFICIENT CLINICAL RESPONSE	5 (10.9)	10 (20.0)
ADVERSE EVENT	4 (8.7)	3 (6.0)
LABORATORY ABNORMALITY	0 (0.0)	0 (0.0)
SPECIAL SAFETY TEST	0 (0.0)	0 (0.0)
SUBJECT DIED	0 (0.0)	0 (0.0)
PROTOCOL VIOLATION	0 (0.0)	0 (0.0)
LOST TO FOLLOW-UP	1 (2.2)	0 (0.0)
DID NOT MEET ENTRANCE CRITERIA	1 (2.2)	0 (0.0)
WITHDREW CONSENT	3 (6.5)	3 (6.0)
OTHER	1 (2.2)	0 (0.0)

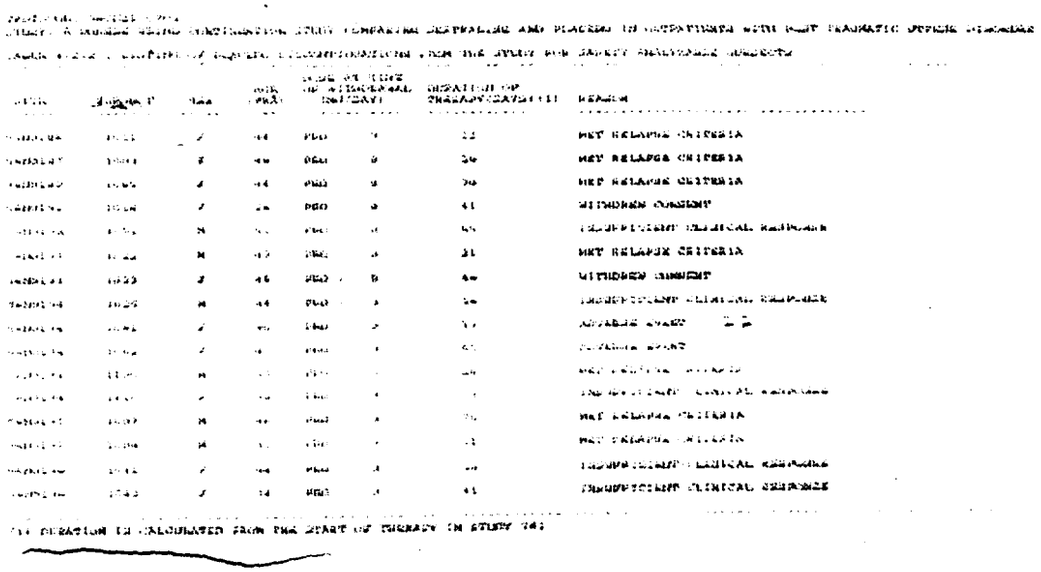
TABLE 4.2.1 : DEATHS OF OMEPRAZOLE DISCONTINUATIONS FROM THE STUDY FOR SAFETY ANALYSABLE SUBJECTS

[illegible]	[illegible]	SEX	AGE AT FIRST	DOSE AT TIME OF WITHDRAWAL (MG/DAY)	DURATION OF THERAPY(DAYS)[1]	REASON
[illegible]	[illegible]	F	47	[illegible]	134	[illegible]
[illegible]	[illegible]	M	41	[illegible]	41	ADVERSE EVENT
[illegible]	[illegible]	F	36	[illegible]	28	WITHDRAWN CONSENT
[illegible]	[illegible]	F	31	[illegible]	35	OTHER, PREGNANCY
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	34	[illegible]	21	NOT MEETING CRITERIA
[illegible]	[illegible]	F	47	[illegible]	4	ADVERSE EVENT
[illegible]	[illegible]	F	38	[illegible]	28	WITHDRAWN CONSENT
[illegible]	[illegible]	F	44	[illegible]	44	ADVERSE EVENT
[illegible]	[illegible]	F	39	[illegible]	183	ADVERSE EVENT
[illegible]	[illegible]	F	36	[illegible]	56	[illegible]
[illegible]	[illegible]	F	43	[illegible]	1	[illegible]
[illegible]	[illegible]	F	37	[illegible]	29	NOT MEETING CRITERIA
[illegible]	[illegible]	F	49	[illegible]	119	[illegible]
[illegible]	[illegible]	F	47	[illegible]	42	[illegible]
[illegible]	[illegible]	F	44	[illegible]	56	NOT MEETING CRITERIA

[1] DURATION IS CALCULATED FROM THE START OF THERAPY IN STUDY THI

TABLE 6.1
TREATMENT EMERGENT SERIOUS ADVERSE EVENTS - ALL CASUALTIES
SERTRALINE PROTOCOL 91-0761
REPORTING PERIOD: CUMULATIVE THROUGH JUNE 3, 1999

ADR CASE NO./ (a) PATIENT IDENTIFIER	COUNTRY	S E X	A G E	R A C E	WEI GHT (KG)	TOTAL DAILY DOSE (mg)	EVENT ONSET DAY (a)	CURR-ENT STOP DAY	APT EVENT TERM	ACTION TAKEN	INVESTIGATOR (CAUSALITY	OUTCOME(S)
TREATMENT: Sertraline Hydrochloride												
PARTICIPANTS:												
7116632 N-0753 1269 96-N-0192	US	F	32	W	65.8	300.00	MG	60	59	FETAL DEATH	LOST THERAPY EVENT - DRUG PERMANENTLY DISCONTINUED	OTHER (Unknown, not study drug related.)	RESOLVED
3002075 N-0753 1254 96-N-0199	US	M	48	W	97.1	100.00	MG	199	N/A	POWER SAW INJURY TO LEFT DORSAL HAND	NO ACTION TAKEN	OTHER (Accidental trauma)	HOSPITALI-ZATION: RESOLVED



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PROTOCOL: 96CE21-0703

STUDY : A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 6.3: INCIDENCE AND SEVERITY OF TREATMENT EMERGENT ADVERSE EVENTS ASSOCIATED WITH DISCONTINUATIONS SUMMARIZED BY TREATMENT GROUP - ALL CAUSALITIES

	INCIDENCE IN SAFETY ANALYZABLE SUBJECTS							
	SERTRALINE				PLACEBO			
ADVERSE EVENT VALUE*	NO. SUBJ. (%)	MILD	MODE RATE	SEV ERE	NO. SUBJ. (%)	MILD	MODE RATE	SEV ERE	P-
TOTAL NO. OF SUBJECTS	46				50				
NO. OF SUBJ. DISCONTINUED DUE TO ADV. EVENT/LABORATORY ABNORMALITY	4(8.7%)				3(6.0%)				0.707
PSYCHIATRIC DISORDERS									
DEPRESSION	1(2.2%)	0	1	0	0(0.0%)	0	0	0	0.479
INSOMNIA	1(2.2%)	1	0	0	0(0.0%)	0	0	0	0.479
AGITATION	0(0.0%)	0	0	0	2(4.0%)	2	0	0	0.496
METABOLIC AND NUTRITIONAL DISORDERS									
WEIGHT INCREASE	1(2.2%)	1	0	0	0(0.0%)	0	0	0	0.479
HEART RATE AND RHYTHM DISORDERS									
PALPITATION	1(2.2%)	1	0	0	0(0.0%)	0	0	0	0.479
BODY AS A WHOLE - GENERAL DISORDERS									
CHEST PAIN	1(2.2%)	0	0	1	0(0.0%)	0	0	0	0.479
SKIN AND APPENDAGES DISORDERS									
SWEATING INCREASED	0(0.0%)	0	0	0	1(2.0%)	0	1	0	1.000

---- (END) ----

NOTE: EACH ADVERSE EVENT WAS TABULATED ONCE PER SUBJECT ON A PREFERRED TERM BASIS. THE MOST SEVERE OCCURRENCE IS SHOWN.

SUBJECT MAY HAVE HAD MORE THAN ONE ADVERSE EVENT LEADING TO DISCONTINUATION.

* FISHER'S EXACT TEST (2-TAIL)

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STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 4.2.1 : LISTING OF SERTRALINE DISCONTINUATIONS FROM THE STUDY FOR SAFETY ANALYZABLE SUBJECTS

SITE	SUBJECT	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (MG/DAY)	DURATION OF THERAPY(DAYS)(1)	REASON
96NO185	1019	F	47	SER - 150	108	INSUFFICIENT CLINICAL RESPONSE
96NO186	1030	M	49	SER - 100	91	ADVERSE EVENT
96NO187	1002	F	35	SER - 200	28	WITHDREW CONSENT
96NO192	1049	F	31	SER - 100	29	OTHER: PREGNANCY
96NO194	1028	M	43	SER - 200	98	INSUFFICIENT CLINICAL RESPONSE
96NO194	1063	F	42	SER - 200	29	MET RELAPSE CRITERIA
96NO194	1064	F	47	SER - 150	4	ADVERSE EVENT
96NO195	1006	F	38	SER - 150	28	WITHDREW CONSENT
96NO198	1101	F	46	SER - 150	65	ADVERSE EVENT
96NO199	1123	F	39	SER - 25	202	ADVERSE EVENT
96NO201	1079	F	34	SER - 150	58	INSUFFICIENT CLINICAL RESPONSE
96NO203	1085	F	33	SER - 200	1	DID NOT MEET ENTRANCE CRITERIA
96NO205	1091	F	37	SER - 150	29	MET RELAPSE CRITERIA
96NO206	2010	F	59	SER - 150	114	INSUFFICIENT CLINICAL RESPONSE
96NO207	1107	F	47	SER - 150	27	INSUFFICIENT CLINICAL RESPONSE
96NO207	1149	F	48	SER - 150	56	MET RELAPSE CRITERIA

(1) DURATION IS CALCULATED FROM THE START OF THERAPY IN STUDY 703

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PROTOCOL: 9GCE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 4.2.2 : LISTING OF PLACEBO DISCONTINUATIONS FROM THE STUDY FOR SAFETY ANALYZABLE SUBJECTS

SITE	SUBJECT	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (MG/DAY)	DURATION OF THERAPY(DAYS)(1)	REASON
96NO186	1031	F	44	PBO - 0	32	MET RELAPSE CRITERIA
96NO187	1003	F	48	PBO - 0	28	MET RELAPSE CRITERIA
9GNO189	1065	F	44	PBO - 0	98	MET RELAPSE CRITERIA
9GNO191	1016	F	26	PBO - 0	41	WITHDREW CONSENT
96NO192	1051	M	53	PBO - 0	55	INSUFFICIENT CLINICAL RESPONSE
96NO193	1022	M	49	PBO - 0	21	MET RELAPSE CRITERIA
96NO193	1023	F	45	PBO - 0	46	WITHDREW CONSENT
96NO194	1025	M	44	PBO - 0	36	INSUFFICIENT CLINICAL RESPONSE
96NO194	1061	F	50	PBO - 0	19	ADVERSE EVENT
96NO194	1062	F	43	PBO - 0	59	ADVERSE EVENT
96NO194	1109	M	39	PBO - 0	28	MET RELAPSE CRITERIA
9GNO194	1110	F	38	PBO - 0	9	INSUFFICIENT CLINICAL RESPONSE
9GNO195	1007	M	46	PBO - 0	70	MET RELAPSE CRITERIA
96NO195	1008	M	39	PBO - 0	31	MET RELAPSE CRITERIA
96NO196	1041	F	44	PBO - 0	38	INSUFFICIENT CLINICAL RESPONSE
96NO196	1042	F	34	PBO - 0	41	INSUFFICIENT CLINICAL RESPONSE

(1) DURATION IS CALCULATED FROM THE START OF THERAPY IN STUDY 703

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PROTOCOL: [illegible]

STUDY: A DOUBLE-BLIND CONFIRMATION STUDY COMPARING CONTINUING AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE [illegible]: SUMMARY OF CHANGE IN CAPS-2 TOTAL, IMPACT OF EVENT SCALE TOTAL, CGI-SEVERITY, CGI-IMPROVEMENT, DAVIDSON SCALE TOTAL, HAM-D, AND Q-LES-Q FROM BASELINE TO ENDPOINT BY TREATMENT GROUP AND BETWEEN-TREATMENT COMPARISONS: INTENT-TO-TREAT FEMALE SUBJECTS

Adjusted Mean Change from Baseline +/- Standard Error

	Sertraline		Placebo		
	N	Mean +/- SE	N	Mean +/- SE	p-value (2)
CAPS-2 (17 Item Total Score)	29	5.4 +/- 3.08	28	22.3 +/- 4.24	0.002
Impact of Event Scale (Total Score)	29	2.2 +/- 1.45	28	7.2 +/- 1.99	0.061
CGI-Severity	29	0.2 +/- 0.24	28	1.2 +/- 0.24	0.004
(CGI-Improvement (1)	29	0.3 +/- 0.22	28	1.3 +/- 0.24	0.005
Davidson Scale (Total Score)	29	9.0 +/- 4.38	27	23.4 +/- 4.81	0.052
HAM-D	25	2.7 +/- 1.91	21	9.9 +/- 2.18	0.015
Q-LES-Q	25	-4.4 +/- 3.44	23	-15.8 +/- 4.32	0.037

(1) CGI-Improvement is assessed relative to the subject's condition at baseline at the feeder studies 401 or 402.

(2) P-values are obtained from the analysis of covariance with treatment, site and baseline values as effects.

PROTOCOL: [illegible]

TITLE: A DOUBLE-BLIND, RANDOMIZATION, STUDY COMPARING [illegible] AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 9.2.3: SUMMARY OF CHANGE IN CAPS-1 TOTAL, IMPACT OF EVENT SCALE TOTAL, CGI-SEVERITY, CGI-IMPROVEMENT, DAVIDSON SCALE TOTAL, HAM-D, AND Q-LES-Q FROM BASELINE TO ENDPOINT BY TREATMENT GROUP AND BETWEEN-TREATMENT COMPARISONS. INTENT-TO-TREAT MALE SUBJECTS

Adjusted Mean Change from Baseline
+/- Standard Error

	Venlafaxine		Placebo		
	N	Mean +/- SE	N	Mean +/- SE	p-value (2)
CAPS-1 (17 Item Total Score)	9	-33.8 +/- 9.11	18	17.5 +/- 5.81	0.018
Impact of Event Scale (Total Score)	9	-7.0 +/- 4.49	18	5.9 +/- 2.76	0.041
CGI-Severity	9	-0.5 +/- 0.45	18	0.5 +/- 0.28	0.066
CGI-Improvement (1)	9	-0.7 +/- 0.42	18	0.1 +/- 0.18	0.033
Davidson Scale (Total Score	9	-8.9 +/- 10.23	18	11.9 +/- 6.42	0.221
HAM-D	9	-1.4 +/- 1.77	18	0.3 +/- 1.21	0.141
Q-LES-Q	9	3.1 +/- 3.91	17	-0.9 +/- 4.05	0.103

(1) CGI-Improvement is assessed relative to the subject's condition at baseline at the feeder studies 471 or 482.

(2) P-values are obtained from the analysis of covariance with treatment, site and baseline values as effects.

TABLE 6.4
TREATMENT EMERGENT SERIOUS ADVERSE EVENTS - ALL CAUSALITIES
SERTRALINE PROTOCOL N-0703
REPORTING PERIOD: CUMULATIVE THROUGH JUNE 4, 1999

* * Copy of table as of 28 September 1999 * *

AEM Case No./ (a)												
Patient Identifier	Country	Sex	Age	Race	Weight (KG)	Total Daily Dose (b)	Event Onset Day (c)	Therapy Stop Day	Event Term	Action Taken	Investigator Causality	Outcome (d)
TREATMENT: Sertraline Hydrochloride												
Pharmaceuticals												
9716632 N - 0703 1049 96 - N - 0192	US	F	32	W	60.8	100.00 MG	60	29	Fetal Death	Post Therapy Event – Drug Previously Discontinued	OTHER (Unknown, not study drug related.)	Resolved
9802075 N - 0703 154 0 - N - 0199	US	M	48	W	97.1	100.00 MG	199	N / A	Power Saw Injury to left dorsal hand	No Action Taken	OTHER (Accidental trauma)	Hospitalization ; Resolved

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i)Inpatient hospitalization or (ii)Prolongation of hospital stay
ND = NOT DONE RACE KEY: W = WHITE A = ASIAN
N/A = NOT AVAILABLE B = BLACK O = OTHER

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SERIOUS ADVERSE EVENTS Page 1 TABLE 6.4
TREATMENT EMERGENT SERIOUS ADVERSE EVENTS - ALL CAUSALITIES
SERTRALINE PROTOCOL N-0672
REPORTING PERIOD: CUMULATIVE THROUGH JUNE 4, 1999
* * Copy of table as of 27 September 1999 *

AEM Case No./ (a)												
Patient Identifier	Country	Sex	Age	Race	Weight (KG)	Total Daily Dose (b)	Event Onset Day (c)	Therapy Stop Day	Event Term	Action Taken	Investigator Causality	Outcome (d)
TREATMENT: Sertraline Hydrochloride												
Pharmaceutica ls												
9704544 N - 0672 7025 95 - N - 0087	US	F	48	W	105.2	200.00 MG	174	N / A	Incisional Hernia	No Action Taken	OTHER (Hernia)	Hospitalization ; Resolved
9703602 N - 0672 8012 96 - N - 0058	US	F	32	B	169.2	50.00 MG	7	N / A	Shortness of Breath; Chest Pain	Dose Temporarily Stopped	Disease Under Study	Hospitalization ; Resolved
9716299 N - 0672 `12 , - N - 0058	US	F	32	B	139.3	100.00 MG	166	165	New Onset of Asthma; Angioedema; Pharyngeal Constriction	Dose Permanently Stopped	Concomitant Treatment (Lotensin)	Hospitalization ; Resolved
9713924 N - 0672 8020 96 - N - 0054	US	F	24	W	107.9	200.00 MG	44	N / A	Right Ovarian Cyst	Dose Temporarily Stopped	OTHER Illness (Recurrent Ovarian Cyst)	Hospitalization ; Resolved

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
- (i)Inpatient hospitalization or (ii)Prolongation of hospital stay
ND = NOT DONE RACE KEY: W = WHITE A = ASIAN
N/A = NOT AVAILABLE B = BLACK O = OTHER

TABLE 6.4
TREATMENT EMERGENT SERIOUS ADVERSE EVENTS - ALL CAUSALITIES
SERTRALINE PROTOCOL N-0672
REPORTING PERIOD: CUMULATIVE THROUGH JUNE 4, 1999
* * Copy of table as of 27 September 1999 * *

AEM Case No./ (a)												
Patient Identifier	Country	Sex	Age	Race	Weight (KG)	Total Daily Dose (b)	Event Onset Day (c)	Therapy Stop Day	Event Term	Action Taken	Investigator Causality	Outcome (d)
TREATMENT: Sertraline Hydrochloride												
Pharmaceuticals												
9709099 N - 0672 8041 96 - N - 0061	US	F	30	B	88.0	100.00 MG	115	N / A	Breast Reduction Surgery	No Action Taken	OTHER (Large Breast)	Hospitalization ; Resolved
9717764 N - 0672 8123 96 - N - 0057	US	F	40	W	89.4	50.00 MG	7	N / A	Basal Cell Carcinoma of the right lower eyelid	No Action Taken	OTHER (Environmental factors)	Event still present, better than onset
9728606 N - 0672 8123 96 - N - 0057	US	F	41	W	90.7	100.00 MG	136	N / A	Bone Graft of the left humerus; removal and replacement intramedullary rod	No Action Taken	OTHER (Motor vehicle accident)	Hospitalization ; Resolved

(a) PROTOCOL/PATIENT ID/GRANT NO./LOCAL COUNTRY NO. - Blank fields suppressed
(b) Closest to onset of event
(c) Days are relative to the day of starting double blind/active therapy (Day 1)
(d) An outcome of "Hospitalization" means the event being reported resulted in either of the following:
(i)Inpatient hospitalization or (ii)Prolongation of hospital stay
ND = NOT DONE RACE KEY: W = WHITE A = ASIAN
N/A = NOT AVAILABLE B = BLACK O = OTHER

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PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER
TABLE 7.1.1: INCIDENCE OF CLINICALLY SIGNIFICANT LABORATORY ABNORMALITIES SUMMARIZED BY TREATMENT GROUP

LABORATORY PARAMETER	CRITERIA FOR ABNORMALITY		ABNORM-ALITY	NUMBER TESTED(1)		NUMBER AND % OF SUBJECTS WITH SPECIFIED CHANGE(2)				P-VALUE(3)
				SERTRALINE	PLACEBO	SERTRALINE		PLACEBO		
HEMATOLOGY										
HGB(HEMOGLOBIN)	<= 9.5(F) 11.5(M)	G/DL	LOW	35	42	0	0.0%	0	0.0%	1.000
HCT(HEMATOCRIT)	<= 32(F) 37(M)	%	LOW	35	42	0	0.0%	1	2.4%	1.000
RBC (RED BLOOD CELLS)	<= 3, >= 6	X10E6/MM3	LOW	35	42	0	0.0%	0	0.0%	1.000
			HIGH	35	42	0	0.0%	0	0.0%	1.000
WBC (WHITE BLOOD COUNT)	<= 2.8, >= 16	X10E3/MM3	LOW	35	42	0	0.0%	0	0.0%	1.000
			HIGH	35	42	0	0.0%	0	0.0%	1.000
NEUTROPHILS	<= 15	%	LOW	35	42	0	0.0%	0	0.0%	1.000
EOSINOPHILS	>= 10	%	HIGH	35	42	1	2.9%	0	0.0%	0.455
PLATELETS	<= 75, >= 700	X10E3/MM3	LOW	35	42	0	0.0%	0	0.0%	1.000
			HIGH	35	42	0	0.0%	0	0.0%	1.000
URINALYSIS										
PROTEIN: URINE	>= 2	UNITS	HIGH	36	41	0	0.0%	1	2.4%	1.000
GLUCOSE: URINE	>= 2	UNITS	HIGH	36	41	0	0.0%	0	0.0%	1.000
LIVER FUNCTION TESTS										
T/PROTEIN	<= 4.5, >= 9	G/DL	LOW	37	41	0	0.0%	0	0.0%	1.000
			HIGH	37	41	0	0.0%	0	0.0%	1.000
ALBUMIN	<= 3.5, >= 6.5	G/DL	LOW	37	41	1	2.7%	0	0.0%	0.474
			HIGH	37	41	0	0.0%	0	0.0%	1.000
T/BILIRUBIN	>= 2	MG/DL	HIGH	37	41	0	0.0%	0	0.0%	1.000
ALK PHOSPHATASE	>= 3.0 X ULN	U/L	HIGH	37	41	0	0.0%	0	0.0%	1.000
SGOT UNITS	>= 3.0 X ULN	U/L	HIGH	37	41	0	0.0%	0	0.0%	1.000
SGPT UNITS	>= 3.0 X ULN	U/L	HIGH	37	41	0	0.0%	0	0.0%	1.000
RENAL FUNCTION TESTS										
BUN	>= 30	MG/DL	HIGH	37	41	0	0.0%	0	0.0%	1.000
CREATININE	>= 2	MG/DL	HIGH	37	41	0	0.0%	0	0.0%	1.000
URIC ACID	>= 8.5(F) 10.5(M)	MG/DL	HIGH	37	41	0	0.0%	0	0.0%	1.000
OTHER										
CHOLESTEROL	>= 330	MG/DL	HIGH	37	41	1	2.7%	0	0.0%	0.474
RANDOM GLUCOSE	>= 140	MG/DL	HIGH	37	41	1	2.7%	1	2.4%	1.000

(1) TOTAL NUMBER OF SUBJECTS WITH AT LEAST ONE OBSERVATION OF THE GIVEN LAB PARAMETER DURING TREATMENT IN STUDY 703.
(2) NUMBER AND % OF SUBJECTS WITH A CLINICALLY SIGNIFICANT ABNORMALITY.
(3) COMPARISON OF INCIDENCE RATES USING THE FISHER'S EXACT TEST (TWO-TAILED).

PROTOCOL: 96CE21-0703

STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 7.2: LABORATORY TEST CHANGES FROM BASELINE TO ENDPOINT SUMMARIZED BY TREATMENT GROUP

	SERTRALINE				PLACEBO				
LABORATORY TEST	N(1)	MEAN BASELINE VALUE	CHANGE FROM BASELINE(2) MEAN	S.D.	N(1)	MEAN BASELINE VALUE	CHANGE FROM BASELINE(2) MEAN	S.D.	P-VALUE**
HEMATOLOGY									
HGB(HEMOGLOBIN)	34	13.89	-0.12	0.64	41	14.31	-0.24	1.03	0.7413
HCT(HEMATOCRIT)	33	42.09	-0.67	2.23	39	43.10	-1.00	3.49	0.6771
RBC (RED BLOOD CELLS)	34	4.66	-0.02	0.23	41	4.71	-0.08	0.32	0.3955
WBC (WHITE BLOOD COUNT)	34	6.76	-0.06	1.29	41	7.46	-0.26	1.66	0.3120
NEUTROPHILS	34	59.97	-1.21	8.81	41	61.49	-0.46	7.05	1.0000
EOSINOPHILS	34	2.14	-0.04	1.10	41	1.80	0.14	1.07	0.9279
PLATELETS	34	254.56	4.59	37.00	41	259.90	2.10	42.67	0.6625
LIVER FUNCTION TESTS									
T/PROTEIN	37	7.28	-0.08	0.40	40	7.30	-0.00	0.42	0.6168
ALBUMIN	37	4.14	0.01	0.24	40	4.28	-0.01	0.28	0.4457
T/BILIRUBIN	37	0.49	-0.01	0.16	40	0.53	0.06	0.19	0.1651
ALK PHOSPHATASE	37	67.89	3.27	11.96	40	64.20	-1.70	9.29	0.0764
SGOT UNITS	37	22.86	-1.16	6.97	40	22.83	-2.20	4.44	0.4194
SGPT UNITS	37	22.54	0.32	11.50	40	23.60	-2.35	6.97	0.4935
RENAL FUNCTION TESTS									
BUN	37	13.24	0.38	3.21	40	13.75	-0.75	2.70	0.1290
CREATININE	37	0.73	0.01	0.14	40	0.79	0.00	0.16	0.7880
URIC ACID	37	4.31	0.21	0.82	40	4.52	0.40	0.90	0.1765
OTHER									
CHOLESTEROL	37	232.16	-4.84	24.34	40	218.90	-11.88	30.55	0.2059
RANDOM GLUCOSE	36	90.19	3.44	17.76	40	87.73	4.85	19.85	0.5357

NOTES: (1) TOTAL NUMBER OF SUBJECTS FOR WHOM LABORATORY TEST VALUES WERE AVAILABLE AT BASELINE OF STUDY 703 AND AT LEAST ONCE DURING TREATMENT IN STUDY 703.

(2) CHANGE FROM BASELINE TO ENDPOINT WAS CALCULATED FOR EACH SUBJECT AND THE MEANS OF THESE CHANGES WERE DETERMINED.

** COMPARISONS OF CHANGES FROM BASELINE USING THE WILCOXON RANK SUM TEST.

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STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 9: INCIDENCE OF USE OF CONCOMITANT MEDICATION SUMMARIZED BY TREATMENT GROUP

	SERTRALINE	PLACEBO
NUMBER OF SUBJECTS	46	50
NUMBER (%) OF SUBJECTS WITH ANY CONCOMITANT MEDICATIONS	42 (91.3%)	39 (78.0%)
NSAID	31 (67.4%)	28 (56.0%)
IBUPROFEN	12	14
ASPIRIN	11	13
ACETAMINOPHEN	13	7
NAPROSYN(NAPROXEN)	4	0
ALEVE	2	1
TYLENOL PM	0	3
MIDOL	1	1
NAPROXEN SODIUM(ANAPROX)	2	0
BAYER ASPIRIN (CHILDREN S)	1	0
INDOMETHACIN	1	0
KETOPROFEN	0	1
NAPRELAN	0	1
TYLENOL COLD MULTI. SYMPTOM	0	1
ANTIBIOTICS	15 (32.6%)	11 (22.0%)
AUGMENTIN	3	3
AMOXICILLIN	3	2
CEPHALEXIN (KEFLEX)	4	1
AZITHROMYCIN (ZITHROMAX)	1	2
ERYTHROMYCIN	2	1
BIAXIN (CLARITHROMYCIN)	0	2
CIPRO	1	1
DOXYCYCLINE	0	2
MINOCYCLINE HCL (MINOCIN)	2	0
ANTIBIOTIC(UNSPECIFIED)	0	1
ANTIBIOTICS UNS	1	0
CEFAZOLIN SODIUM(ANCEF)(KEFZOL)	1	0
CLEOCIN.T-TOPICAL	1	0
ERYTHROMYCIN CREAM 2%	1	0
FLOXIN	1	0
FLUCONAZOLE	0	1
METRONIDAZOLE	1	0
PEN V K	0	1
PENICILLIN	1	0
SPORNAX	1	0

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PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 9: INCIDENCE OF USE OF CONCOMITANT MEDICATION SUMMARIZED BY TREATMENT GROUP

	SERTRALINE	PLACEBO
ANTIBIOTICS		
TETRACYCLINE HYDROCHLORIDE	1	0
ENDOCRINE	15 (32.6%)	19 (38.0%)
ESTROGENS, CONJUGATED	4	5
FLONASE	2	2
FLUTICASONE PROPIONATE	2	2
PROVERA	1	3
DEPO-PROVERA	1	2
ESTROGEN	2	1
BECLOMETHASONE DIPROPIONATE	1	1
LO/OVRAL	2	0
MEDROXYPROGESTERONE ACETATE (AMEN)	2	0
PROGESTERONE	0	2
BETAMETHASONE VALERATE - VALISONE	0	1
BIRTH CONTROL PILLS(GENERAL)	0	1
ESTRATEST	0	1
ESTROPIPATE (OGEN)	0	1
ESTROSTEP	0	1
FLUNISOLIDE	1	0
GEMFIBROZIL (LOPID)	1	0
HYDROCORTISONE CREAM 1.0%	0	1
HYDROCORTISONE CREAM 2.5%	1	0
METHYLPREDNISOLONE	1	0
NORDETTE-28	0	1
ORTHO TRI-CYCLEN	1	0
STEROID INJECTION	1	0
ANTIHISTAMINES	10 (21.7%)	6 (12.0%)
CLARITIN	5	1
LORATADINE	2	1
CLARITIN-D	2	0
DIPHENHYDRAMINE	1	1
DIPHENHYDRAMINE HYDROCHLORIDE	2	0
ALLEGRA	1	0
CETIRIZINE (UCB-P071)	0	1
CETIRIZINE (ZYRTEC)	0	1
CHLORPHENIRAMINE	0	1
TAVIST-1	0	1

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PROTOCOL: 96CE21-0703
STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 9: INCIDENCE OF USE OF CONCOMITANT MEDICATION SUMMARIZED BY TREATMENT GROUP

	SERTRALINE	PLACEBO
COLD/FLU REMEDIES	6 (13.0%)	12 (24.0%)
GUAIFENESIN	1	2
PSEUDOEPHEDRINE HYDROCHLORIDE	1	1
TYLENOL ALLERGY SINUS	0	2
AFRIN NASAL SPRAY	0	1
ALKA-SELTZER+COLD MEDICINE	0	1
ALKASELTZER PLUS	0	1
BENZONATATE (TESSALON PERLES)	0	1
CONTAC	1	0
DAYQUIL LIQUICAPS	0	1
DECONAMINE-SR	0	1
DEXTROMETHORPHAN HYDROBROMIDE	0	1
DIMETAPP	0	1
ENTEX-LA	0	1
GUAIFENESIN LA	0	1
ROBITUSSIN	0	1
ROBITUSSIN DM	1	0
TYLENOL ALLERGY MAXIMUM STRENGTH	1	0
TYLENOL SINUS MEDICATION	1	0
GI	6 (13.0%)	6 (12.0%)
PEPTO-BISMOL	2	2
RANITIDINE HCL	2	1
KAOPECTATE	0	2
LOPERAMIDE HCL (IMODIUM)	1	1
FAMOTIDINE	1	0
IMODIUM AD	0	1
MAALOX	0	1
PRILOSEC (OMEPRAZOLE)	1	0
ANALGESIC	5 (10.9%)	3 (6.0%)
MEPIVACAINE HCL (CARBOCAINE HCL)	1	1
TYLENOL W/ CODEINE	2	0
ACETAMIN. W/CODEINE	1	0
ACETAMINOPHEN WITH OXYCODONE	1	0
ANESTHETICS, GENERAL	1	0
ANESTHETICS, LOCAL	0	1
DARVOCET-N	0	1
OXYCODONE HYDROCHLORIDE	1	0

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TABLE 9: INCIDENCE OF USE OF CONCOMITANT MEDICATION SUMMARIZED BY TREATMENT GROUP

	SERTRALINE	PLACEBO
CARDIOVASCULAR	5 (10.9%)	2 (4.0%)
ATENOLOL	1	1
LIPITOR	1	1
AMLODIPINE BESYLATE (NORVASC)	1	0
CARDIZEM	0	1
DILTIAZEM	1	0
DYAZIDE	1	0
FUROSEMIDE	1	0
HYDROCHLOROTHIAZIDE	1	0
VERAPAMIL HCL	0	1
ZESTRIL	1	0
CNS	3 (6.5%)	5 (10.0%)
CHLORAL HYDRATE	1	3
ATIVAN	1	0
FLEXERIL	0	1
INVEST. DRUG-NEFAZODONE	0	1
SKELAXIN (METAXALONE)	1	0
MISCELLANEOUS	21 (45.7%)	16 (32.0%)
MULTIVITAMINS (UNSPECIFIED)	9	5
VITAMIN C ASCORBIC	1	3
VITAMIN E	0	4
BACTRIM	1	1
CALCIUM TABLETS	1	1
IRON SUPPLEMENT	0	2
SELENIUM	0	2
VITAMIN B COMPLEX	1	1
ADAPALENE	1	0
ALBUTEROL	0	1
ALBUTEROL INHALER (PROVENTIL INHALER)	0	1
ALLERGY SHOT(UNSPECIFIED)	1	0
CENTRUM SILVER	1	0
CENTRUM VITAMINS	1	0
DITROPAN	1	0
DOVONEX OINTMENT	0	1
EXOREX OINTMENT	0	1
FOLIC ACID	1	0
GINKGO BILOBA PLUS	1	0
IPRATROPIUM BROMIDE	1	0
NASALCROM	0	1

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STUDY: A DOUBLE-BLIND CONTINUATION STUDY COMPARING SERTRALINE AND PLACEBO
IN OUTPATIENTS WITH POST-TRAUMATIC STRESS DISORDER

TABLE 9: INCIDENCE OF USE OF CONCOMITANT MEDICATION SUMMARIZED BY TREATMENT GROUP

	SERTRALINE	PLACEBO
MISCELLANEOUS		
NICODERM-PATCH	1	0
ORPHENADRINE CITRATE	0	1
PERIDEX(CHLORHEXIDINE GLUCONATE)	0	1
PREPARATION H	0	1
QUININE SULFATE	1	0
TETANUS SHOT	1	0
TRIVALENT TYPE A + B	0	1
VANCENASE AQ SPRAY	0	1
VEGETABLE ESTROGEN (TOPICAL)	1	0
VENTOLIN INHALER	1	0
VITAMIN A	0	1
VITAMIN B	0	1
VITAMIN B6 (PYRIDOXINE HYDROCHLORIDE)	1	0
VITASANA	0	1

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/s/

Earl Hearst
1/12/01 10:23:48 AM
MEDICAL OFFICER

Thomas Laughren
2/3/01 10:07:14 AM
MEDICAL OFFICER
I agree that this supplement is approvable. See memo to file for more detailed comments.--TPL

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